FDA Executive Summary

Prepared for the
May 7, 2014 meeting of the
Circulatory System Devices Panel

Classification of the Membrane Lung for Long-term Pulmonary Support [Extracorporeal Membrane Oxygenator – ECMO (21 CFR 868.5610)]

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Overview

On September 12, 2013 the Circulatory System Devices Advisory Committee was convened to discuss the classification of the membrane lung for long-term pulmonary support [extracorporeal membrane oxygenation (ECMO)] (21 CFR 868.5610).

A membrane lung for long-term pulmonary support (21 CFR 868.5610) is the name given to the oxygenator component of an extracorporeal circuit used during long-term procedures, commonly referred to as extracorporeal membrane oxygenation, or ECMO. An ECMO procedure, in current clinical practice, provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood during conditions consistent with acute respiratory and/or cardiorespiratory failure, and comprises several devices (similar to a cardiopulmonary bypass circuit), including (but not limited to) an oxygenator, pump, cannula, heat exchanger, tubing, filters, various monitors/detectors and other accessories.

The information presented to the Advisory Committee Panel (Panel) was primarily related to pediatric (including neonates/infants/pediatric) pulmonary use and failure to wean from bypass. During the Advisory Committee discussions, the Panel put forward their preference for FDA to convene another Panel to include discussions around current clinical uses of ECMO for adult pulmonary and cardiorespiratory indications, when considering a final classification for the 21 CFR 868.5610 regulation. The Panel indicated that clinical use of ECMO in adults has increased in recent years, and is also being used in cases of cardiac failure in all patient populations. As such, the Panel requested that the Food and Drug Administration (FDA) also review the available literature in the adult population, and include this information when considering the overall classification proposal for the membrane lung for long-term pulmonary support (21 CFR 868.5610).

As such, on May 7, 2014, FDA will convene the Circulatory System Devices Advisory Committee to discuss the classification of the membrane lung for long-term pulmonary support (21 CFR 868.5610), specifically for adult pulmonary and cardiopulmonary indications. The membrane-lung for long-term pulmonary support is one of the remaining pre-amendment class III medical devices currently cleared for marketing through the 510(k) pathway. A membrane-lung for long-term pulmonary support, as defined in the current regulation, is a device used to provide to a patient extracorporeal blood oxygenation for longer than 24 hours.

The Panel will be asked to discuss the risks to health of the device type; available scientific evidence, including safety and effectiveness information, with respect to the adult pulmonary and cardiopulmonary indications; and whether special controls, in addition to general controls may be established to provide a reasonable assurance of the safety and effectiveness of the device type, or whether these indications should remain in class III.

ECMO 515(i) Panel Meeting September 12, 2013

On January 8, 2013, FDA issued a proposed order (78 FR 1158) recommending that the current regulation for membrane lung devices for long-term pulmonary support should be redefined to include all components of an extracorporeal circuit for long-term use (ECMO). Furthermore, FDA proposed that these devices be reclassified from class III (PMA) to class II (Special Controls) for conditions where imminent death is threatened by cardiopulmonary failure in

neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery.

On September 12, 2013, FDA and the Circulatory System Devices Advisory Committee convened to discuss the classification of the membrane lung for long-term pulmonary support (21 CFR 868.5610) in the pediatric cardiopulmonary and failure-to-wean patient populations. The Panel discussion involved making recommendations regarding regulatory classification to either reconfirm to class III or reclassify to class I or class II. To this end, the Panel was asked to provide input on the risks to health, safety, and effectiveness of extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support in the pediatric patient population. The panel was requested to weigh in on the FDA's proposed premarket regulatory classification strategy for extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support which included reclassification from Class III to Class II for conditions where an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by respiratory failure (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in pediatric patients.

The Panel agreed with the reclassification proposal to Class II for the pediatric population as identified above, but recommended that FDA convene another Panel to discuss the clinical uses of ECMO for adult pulmonary and cardiopulmonary indications. The Panel requested that FDA review the available literature in the adult population, and include this information when considering the overall classification proposal for the membrane lung for long-term pulmonary support (21 CFR 868.5610).

Current Regulation

21 CFR 868.5610, membrane lung for long-term pulmonary support refers to the oxygenator component of an extracorporeal circuit for long-term procedures, commonly referred to as ECMO. However, many components make up the extracorporeal circuit for ECMO use. Currently, there are no regulations defining the other extracorporeal circuit components that comprise an ECMO circuit (long-term durations of use). Additionally, the membrane lung for long-term pulmonary support is currently defined very narrowly in terms of both intended use (gas exchange only), and technology (membrane oxygenator only):

§ 868.5610 Membrane Lung for Long-Term Pulmonary Support

a) *Identification*: A membrane lung for long-term pulmonary support is a device used to provide to a patient extracorporeal blood oxygenation for longer than 24 hours.

As such, in the proposed order (78 FR 1158, January 8, 2013), the Center for Devices and Radiological Health (CDRH) proposed a classification regulation to include 1) all of the circuit components/accessories needed for long-term extracorporeal support, and 2) flexibility for current technology, to provide an efficient approach to regulate an entire system that

provides and/or participates in long-term extracorporeal support. To achieve this, CDRH proposed the following:

1) Renaming the title of the classification regulation:
    a. FROM: *Membrane Lung for Long-Term Pulmonary Support*
    b. TO: *Extracorporeal Circuit and Accessories for Long-Term Pulmonary/Cardiopulmonary Support*.

2) Moving the regulation from an anesthesiology device regulation (i.e., 868.5610) to a cardiovascular device regulation (870.4100) due to the fact that all of the devices utilized in an ECMO circuit are currently reviewed under cardiovascular regulations (i.e., cardiopulmonary bypass devices).

3) Defining "long-term" as extracorporeal support > 6 hours (i.e., anything beyond typical cardiopulmonary bypass support [≤6 hours] instead of > 24 hours.

The membrane lung for long-term pulmonary support devices, referred to as extracorporeal membrane oxygenation, hereinafter referred to as ECMO, are one of the remaining preamendment class III medical devices currently cleared for marketing through the premarket notification [510(k)] pathway.

Requested Panel Input

FDA is holding this classification panel meeting to obtain comments and recommendations from the panel regarding whether ECMO should remain in class III (subject to PMA) or be reclassified to class II (subject to 510(k)) for the adult pulmonary and cardiopulmonary uses.

As discussed in the Introduction & Regulatory Reference Sheet provided, CDRH is requesting that the panel consider the risks to health for the extracorporeal circuit and accessories for long-term pulmonary support as a class, and determine whether the information available (for the adult patient population), which is subsequently discussed, fits the following criteria:

(i) The information represents valid scientific evidence (according to 21 CFR 860.7) that is adequate to demonstrate a reasonable assurance of safety and effectiveness for the device type; and whether
(ii) Special controls can be appropriately established to mitigate the identified risks to health.

The Panel is tasked with discussing whether the risks to health for the extracorporeal circuit and accessories for long-term pulmonary or cardiopulmonary support have been appropriately identified. Further, the panel will be asked to discuss the available scientific evidence for the currently-marketed technologies, indications, and clinical use.

As defined in 21 CFR 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. As defined in 21 CFR

860.7(e)(1), there is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

If a recommendation of class III is made, each device and accessory would be expected to provide an independent dataset to demonstrate a reasonable assurance of safety and effectiveness prior to marketing the device. The collection of such data translates into establishing an initial knowledge basis of safety and effectiveness information on which to rely. class III devices, regulated through the PMA program, can be considered for reclassification at a later date once a valid scientific body of evidence has been collected to establish safety and effectiveness and special controls can be established to mitigate risks.

If a recommendation of class II is made, then it should be noted that it is the current body of evidence considered as part of this panel meeting that will be leveraged to support future substantially equivalent determinations through the 510(k) program. Special controls would be established to provide assurance through mitigating known risks that any new devices coming to market through the 510(k) program are "as safe and effective" as the predicate(s) (Refer to Section 513(i)(1)(A) of the FD&C Act).

Device/Circuit Description

A membrane lung for long-term pulmonary support (21 CFR 868.5610) is the name given to the oxygenator component of an extracorporeal circuit used during long-term procedures, commonly referred to as extracorporeal membrane oxygenation, or ECMO. An ECMO procedure, in current clinical practice, provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood during conditions consistent with respiratory or cardiorespiratory failure, usually in cases where the patient is unresponsive to optimal ventilation and/or pharmacologic management. An ECMO circuit (similar to a cardiopulmonary bypass circuit) comprises several devices (not necessarily cleared or approved for ECMO), including (but not limited to) an oxygenator, pump, cannula, heat exchanger, tubing, filters, various monitors/detectors and other accessories.

An example of an ECMO circuit is shown below:

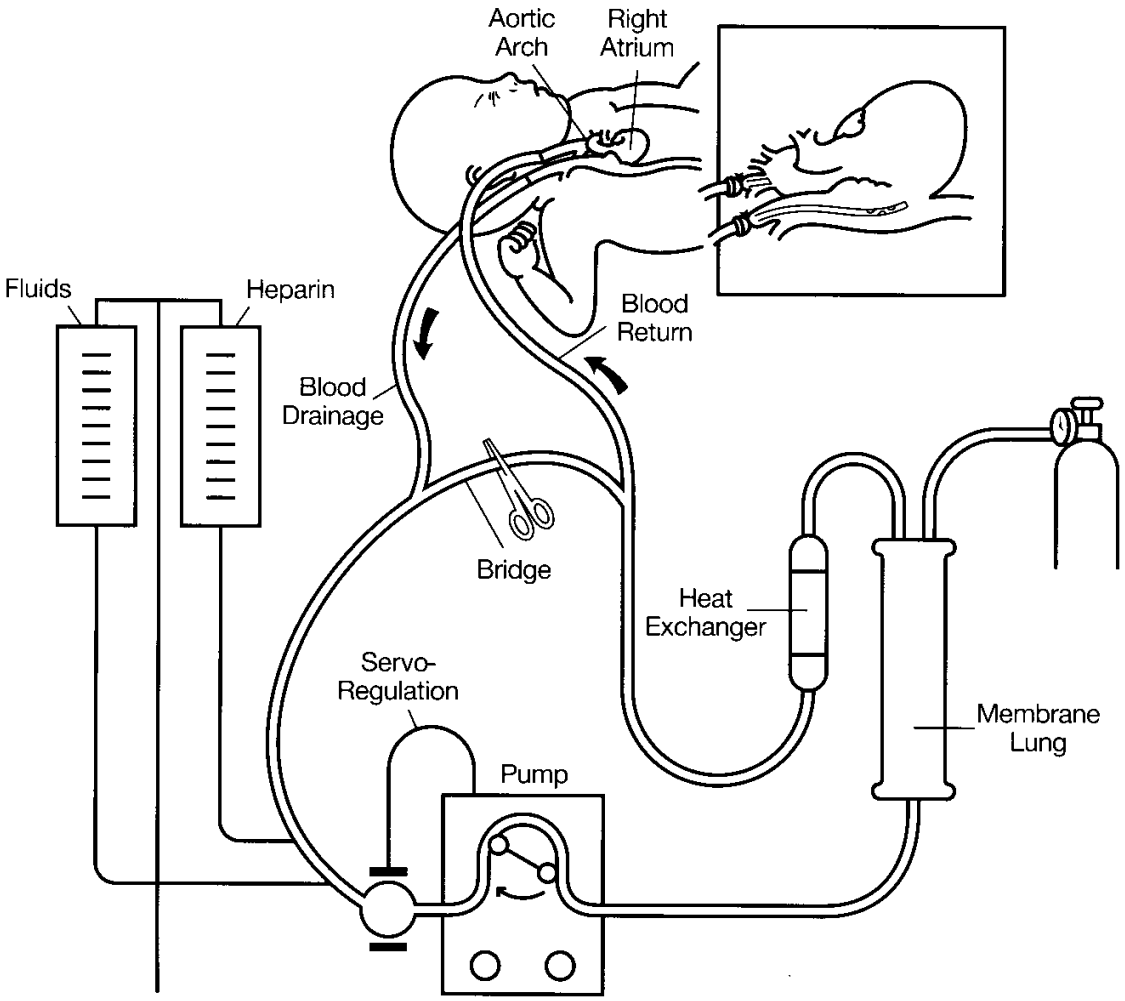

Figure 1: ECMO Circuit *(Source: Google Images)*

The regulation for membrane lung for long-term pulmonary support (21 CFR 868.5610) describes a specific gas exchange technology which includes the use of a membrane (e.g., silicone) that acts as a barrier between the blood flow and gas flows, but also has the ability to diffuse oxygen and carbon dioxide through the membrane based on pressure gradients – i.e., oxygen diffuses into the blood through the membrane because the pressure gradient for oxygen is higher on the gas side of the membrane, and carbon dioxide diffuses through the membrane from the blood because the pressure gradient for carbon dioxide is higher on the blood side of the membrane. This procedure enables the patient's circulating blood to continue physiologic gas exchange (using an extracorporeal circuit) when a certain condition prevents their own body from providing the physiologic gas exchange needed to sustain life.

Depending on the patient and condition being treated, the circuit components and circuit configuration (e.g., arterio-venous, veno-venous) may vary. Currently, there are no classification regulations for the long-term use of any of the extracorporeal circuit components used for ECMO, except for the oxygenator component, *21 CFR 868.5610 Membrane lung for long-term*

pulmonary support. There are regulations for each of the components used for ECMO, but currently they are defined only for short-term durations associated with cardiopulmonary bypass procedures (≤6 hours). Because the oxygenator cannot achieve the desired clinical therapy without the other circuit components, all of the device components used for ECMO are being considered in the scope of this classification strategy.

Regulatory/Review History and Indications for Use for 21 CFR 868.5610

Clearance under the 21 CFR 868.5610 regulation:
(Note: The information presented here with respect to previously cleared devices is identical to the information presented in the Executive Summary prepared for the September 12, 2013 Panel.)[a]

The devices that have been cleared with ECMO indications have been cleared under several different classification regulations. Part of our regulatory strategy is to ensure that there is consistency in review for the devices intended for ECMO, including 1) a consistent identification for the regulation that includes all of the devices/accessories necessary to perform ECMO, 2) defining long-term cardiopulmonary support as > 6 hours of support (since the same devices used for cardiopulmonary bypass are intended for short-term ≤ 6 hours of support), and 3) having all components used in ECMO procedures under one regulation and classified consistently based on current knowledge of the safety and effectiveness information available. Our regulatory strategy also takes into consideration the fact that all products intended for use in an ECMO circuit are devices that are currently on the market for short-term cardiopulmonary bypass procedures as Class II devices.

The membrane lung for long-term pulmonary support devices, are one of the remaining pre-amendment Class III medical devices currently cleared for marketing through the premarket notification [510(k)] pathway. This device type is a pre-amendment Class III device, meaning that this device type was marketed prior to the Medical Device Amendments of 1976 and was classified by the original classification panels as Class III, but for which FDA never established an effective date for the requirement for premarket approval (PMA). These devices were originally identified as a specific type of oxygenator (membrane technology vs. bubble technology, for example) designed to provide extracorporeal blood oxygenation for > 24 hours. The product code given to the membrane lung for long-term pulmonary support is **BYS** and there has been one (1) 510(k) submission for tubing (see immediately below) cleared under this classification regulation with this product code.

Tubing

K770720 (cleared August 4, 1977 under 21 CFR 868.5610 membrane lung for long-term pulmonary support, product code **BYS**, Class III).

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[a] FDA Executive Summary for the September 12, 2013 Circulatory System Devices Panel meeting is available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM367600.pdf.

Cleared Indications:

> The "William Harvey Extracorporeal Tubing Pack" was originally cleared as tubing for roller pumps. No specific indications for use statement was found since this was before CDRH was requesting Indications for Use forms.

K770720 was updated in Feb 1997 and included the following indications for use statement in the product labeling:

> *"This Bard Vascular Systems Extracorporeal Perfusion Pack is indicated for use during cardiopulmonary bypass procedures and constitutes the extracorporeal circuit in whole or part."*

Other ECMO Clearances

Many components make up the extracorporeal circuit for ECMO use. As such, a review history for devices that have been cleared with long-term/ECMO labeling include cardiopulmonary bypass devices and diagnostic intravascular catheters. Examples are provided immediately below:

Oxygenator

K863476 (cleared November 25, 1986 under 21 CFR 870.4350 Cardiopulmonary Bypass Oxygenator, product code DTZ, Class III [at the time][b])

Cleared Indications:

> *"SciMed Membrane Oxygenators are intended for use in an extracorporeal perfusion circuit for the oxygenation of and the removal of carbon dioxide from the blood."*

The manufacturer added the following statements to the labeling in K863476 for ECMO use:

> *"For prolonged bypass (> 6 hours), or other long-term applications such as ECMO, the following information must be considered:*
>
> - *ECMO applications require technical personnel adequately trained in ECMO methodology.*
> - *The SciMed membrane oxygenator has been used without complication for up to 32 days. Technical complications during long-term use are generally due to ineffective anticoagulation, which reduced oxygenator efficiency. Procedures lasting > 6 hours should include monitoring of blood compartment pressure drop and whole blood coagulation times, and inspection for thrombus formation and system component*

[b] 21 CFR 870.4350 Cardiopulmonary Bypass Oxygenator was reclassified in 2001 from Class III to Class II with Special Controls.

wear.

- *Condensate/water droplets may appear in the gas outlet port area; this has no significant effect on oxygenator performance.*
- *When normothermic perfusion is used for ECMO, the heat exchanger can be connected to the arterial side (outlet) of the oxygenator; arterial blood should enter the top of the heat exchanger.*
- *Use distilled or deionized water in the water bath circuit."*

Heat Exchangers

K884560 (cleared April 3, 1989 under 21 CFR 870.4240 Cardiopulmonary bypass heat exchanger, product code DTR, Class II)

ECMOtherm Heat Exchangers (SciMed):

Cleared Indications:

"The ECMOtherm heat exchanger is intended to be used in neonatal and pediatric ECMO procedures as an integral component in the extracorporeal circuit to maintain normothermia."

K873699 (cleared December 2, 1987 under 21 CFR 870.4240 Cardiopulmonary bypass heat exchanger, product code DTR, Class II)

Seabrook Medical Blood Warming Unit

Cleared Indications:

No specific "indications for use" statement was found (this was before FDA required Indications for Use Forms), however the labeling states that the Seabrook Medical Blood Warming Unit was designed specifically for ECMO procedures to treat cardiorespiratory insufficiency.

Cannula/Catheter

K895352 (cleared November 29, 1989 under 21 CFR 870.4210 Cardiopulmonary bypass catheter, cannula, tubing. product code DWF, Class II)

Kendall 14Fr Veno-venous Dual-Lumen Infant ECMO Catheter

Cleared indication:

"The Kendall Dual-Lumen ECMO cannula is intended to be used as a single cannula for both venous drainage and reinfusion of blood in the right atrium, via the internal jugular vein during ECMO procedures."

K003288 (cleared June 8, 2001 under 21 CFR 870.1200 Diagnostic intravascular catheter, product code GBK, Class II)

Origen – Dual Lumen Cannulas - 12Fr and 15Fr

Cleared indication:

"The OriGen Dual Lumen Cannula is indicated for the simultaneous drainage and reinfusion of blood through the internal jugular vein during ECMO procedures."

K081820 (cleared October 6, 2008 under 21 CFR870.4210 Cardiopulmonary bypass catheter, cannula, tubing. Product code DWF, Class II)

Avalon Elite Bi-Caval Dual Lumen Catheter

Cleared indication:

"The Avalon Elite Bi-Caval Dual Lumen Catheter is intended for use as a single catheter for both venous drainage and reinfusion of blood via the internal jugular vein during extracorporeal life support procedures."

Classification History for 21 CFR 868.5610

A brief summary of the classification history for membrane lung devices for long-term pulmonary support devices is provided within this section.

1979 Proposed Rule and 1982 Final Rule

November 2, 1979 Proposed Rule (44 FR 63387)

This rule proposed membrane lung devices for long-term pulmonary support (i.e., ECMO) be classified into Class III (pre-market approval), because "…insufficient information exists to determine the adequacy of general controls, or to establish standards, to provide reasonable assurance of the safety and effectiveness of this device which is both life-sustaining and life-supporting." The Anesthesiology Device Classification Panel identified the following risks to health associated with the device:

- Thrombocytopenia leading to a tendency of increased bleeding;
- Hemolysis;
- Biocompatibility; and
- Inadequate gas exchange.

Comments regarding this proposal were requested by January 2, 1980.

July 16, 1982 Final Rule (47 FR 31130)

No comments were received by January 2, 1980, so the proposed classification (Class III) was finalized. Membrane lung for long-term support was classified under 21 CFR Part 868 Anesthesiology Devices, Subpart F – Therapeutic Devices, 868.5610:

§ 868.5610 Membrane lung for long-term pulmonary support.

(a) Identification. A membrane lung for long-term pulmonary support is a device used to provide to a patient extracorporeal blood oxygenation for longer than 24 hours.

(b) Classification. Class III (premarket approval).

In 1987, FDA published a clarification in the codified language stating that no effective date had been established for the requirement for premarket approval for the membrane lung for long-term pulmonary support (52 FR 17735, May 11, 1987).

1995 515(i) Order (Call for Information) and 1998 Citizens Petition

August 14, 1995 - 515(i) Order (60 FR 41984)

This Order required the manufacturers of 27 Class III devices (including membrane lung devices for long-term pulmonary support (21 CFR 868.5610)), to submit to FDA (by August 14, 1996) a summary of "…all information known or otherwise available to them respecting such devices, including adverse safety or effectiveness information concerning the devices…in order to determine…whether the classification of the device should be revised, or whether a regulation requiring the submission of premarket approval applications (PMAs) for the device should be promulgated." Based on preliminary information, FDA identified the membrane lung for long-term pulmonary support (21 CFR 868.5610) as one of 27 remaining Class III devices not likely to be reclassified and most likely to require the submission of PMAs in the future.

February 13, 1998 Citizen's Petition - response to 60 FR 41984 (updated 62 FR 32352 to modify required response date from August 14, 1996 to February 14, 1998)

A Citizen's Petition recommending reclassification of the membrane lung for long-term pulmonary support (21 CFR 868.5610) from Class III to Class II, was submitted by a trade organization.

All risks identified in the original proposed rule (44 FR 63387, 1979) and additional risks identified by the submitter (see Discussion of Risks to Health section below) were addressed through proposed special controls.

No final rule was issued following the August 14, 1995 (amended June 13, 1997) FR Notice calling for information related to the classification of membrane lung devices for long-term pulmonary support (21 CFR 868.5610).

2009 515(i) Order (Call for Information) for Remaining Class III Pre-Amendments Devices

April 9, 2009 515(i) Order (74 FR 16214)

FDA issued an order requiring the manufacturers of the remaining Class III devices (including 868.5610 membrane lung for long-term pulmonary support) "…for which regulations requiring submission of premarket approval applications (PMAs) have not been issued…" to submit a summary of "…information known or otherwise available to them respecting such devices, including adverse safety or effectiveness information concerning the devices … in order to determine…whether the classification of the device should be revised to require the submission of a PMA or a notice of a completion of a Product Development

Protocol (PDP), or whether the device should be reclassified into Class I or II." This information was requested to be submitted by August 7, 2009.

Industry Response

August 6, 2009 - Response to April 9, 2009 515(i) Call for Information - Medtronic Cardiovascular, Inc.

Medtronic submitted a response to the April 9, 2009 order for 21 CFR 868.5610 membrane lung for long-term pulmonary support. The information consisted of a copy of the previous citizen's petition (February 13, 1998), along with some updated information (no new risks to health were identified) and a new MDR analysis (see Summary of Evidence Section below). Medtronic is again suggesting that the devices (i.e., oxygenators) be reclassified into Class II (Special Controls), based on the history of the device, the proposed special controls to mitigate the list of risks associated with the device (the same special controls identified in the 1998 citizen's petition), and 30+ year data from the ELSO Registry providing clinical information related to ECMO for all indications/conditions.

January 8, 2013 Proposed Order: Reclassification of the Membrane Lung for Long-Term Pulmonary Support

January 8, 2013 – Proposed Order (78 FR 1158).

FDA issued a proposed order recommending that the current regulation for membrane lung devices for long-term pulmonary support should be redefined to include all components of an extracorporeal circuit for long-term use (ECMO). Furthermore, FDA proposed that these devices be reclassified from class III (PMA) to class II (Special Controls) for conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery.

Responses to this proposal were requested by April 8, 2013.

Industry Response

Comments were received from three sources:

1. 1 of 3 agreed with FDA's proposed reclassification of 21 CFR868.5610;
2. 1 of 3 requested clarification in the scope of the patient population and definitions identified for reclassification; and
3. 1 of 3 was concerned with the proposed regulation, processes, and scope in terms of the requirements for and the regulation of the new technology and expanded clinical use of ECMO for new unproven uses.

A detailed discussion of these comments can be found in the FDA Executive Summary for the September 12, 2013 Circulatory System Devices Panel meeting where the pediatric uses of ECMO were discussed[a].

September 12, 2013 Circulatory System Devices Panel

On September 12, 2013, the Food and Drug Administration (FDA) and the Circulatory System Devices Advisory Committee convened to discuss the classification of the membrane lung for long-term pulmonary support (21 CFR 868.5610) in the pediatric pulmonary and failure-to-wean patient populations. The Panel discussion included making recommendations regarding regulatory classification to either reconfirm to class III or reclassify to class I or class II. To this end, the Panel was asked to provide input on the risks to health, safety, and effectiveness of extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support in the identified populations. The Panel was requested to discuss the FDA's proposed premarket regulatory classification strategy for extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support which included reclassification from class III to class II for conditions where an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by respiratory failure (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in pediatric patients.

The panel agreed with the reclassification proposal and proposed special controls for a class II recommendation for the pediatric population as identified below:

FDA Proposed Regulation and Classification for ECMO devices

21 CFR 870.4100 *Extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support*:

(a) *Identification*. An extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support (>6 hours) is a system of devices that provides assisted extracorporeal circulation and physiologic gas exchange of the patient's blood where an acute (reversible) condition prevents the patient's own body from providing the physiologic gas exchange needed to sustain life in conditions where imminent death is threatened by respiratory failure (e.g., meconium aspiration, congenital diaphragmatic hernia, pulmonary hypertension) in neonates and infants, or cardiorespiratory failure (resulting in the inability to separate from cardiopulmonary bypass following cardiac surgery) in all pediatric patients. An acute reversible or treatable cause of respiratory or cardiorespiratory failure should be evident, and the subject should demonstrate unresponsiveness to maximum medical and/or ventilation therapy. The main components of the system include, but are not limited to, the console (hardware), software and disposables, including but not limited to, an oxygenator, blood pump, heat exchanger, cannulae, tubing, filters, and other accessories (e.g., monitors, detectors, sensors, connectors).

(b) Class II (special controls). The special controls for this device are:

- the design characteristics of the device must ensure that the geometry and design parameters are consistent with the intended use;

- the device(s) must be demonstrated to be biocompatible;

- sterility and shelf-life testing must demonstrate the sterility of patient-contacting components and the shelf-life of these components;

- non-clinical performance evaluation of the device must demonstrate substantial equivalence in terms of safety and effectiveness for performance characteristics on the bench, mechanical integrity, EMC (where applicable), software, durability and reliability, etc.

- In vivo evaluation of the device must demonstrate device performance over the intended duration of use and for the specific indication; and

- labeling must include a detailed summary of the non-clinical and clinical evaluations pertinent to use of the device and adequate instructions with respect to anticoagulation, circuit set up, performance characteristics with respect to compatibility with other circuit components, and maintenance during a procedure.

Discussion of Risks to Health

In **Table 1** below, FDA has identified the risks to health generally associated with the use of an extracorporeal circuit for long-term pulmonary support (including a membrane lung for long-term pulmonary support [21 CFR868.5610], as well as other components needed in the extracorporeal circuit). *Note: These are the same risks as those presented at the September 12, 2013 Panel meeting, with specific examples of adverse events suggested by the Panel:*

- All *italicized information* was prepared from the list of risks identified by the original classification panel as stated in the original proposed rule – November 2, 1979 (44 FR 63387) – Proposed Rule Classification of Membrane Lung for Long-Term Pulmonary Support.

- All risks identified in normal font are the additional risks noted in the February 13, 1998 Citizen's Petition – response to 60 FR 41984 [updated 62 FR 32352] call for information.

- All risks in **bold** font are additional risks identified for the proposed expanded identification for 21 CFR8670.4100 Extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support.

TABLE 1: ECMO Risks to Health

RISKS to HEALTH	
Thrombocytopenia	*Blood platelets important to the clotting cascade may be damaged by use of the device, resulting in a tendency toward increased bleeding (e.g., need for transfusion)***.
Hemolysis	*Red blood cells may be damaged by mechanical, material, or surface features of the extracorporeal circuit (e.g., renal dysfunction)***.
*Adverse Tissue Reaction**	*The patient-contacting materials of the device may cause an adverse immunological or allergic reaction in a patient if the materials are not biocompatible (e.g., inflammatory response)***.
Inadequate Gas Exchange	*Design flaws or mechanical failure of the oxygenator may result in inadequate gas exchange.*[1]
Gas Embolism	Air may be introduced into the extracorporeal circuit and result in a gaseous embolism.
Mechanical Failure [2]	Design flaws, mechanical integrity concerns, weakness in the connections or construction of the circuit components could lead to breaches in the circuit (leaks), performance failures, blood loss, etc., over the intended duration of use.[3]
Hemorrhage	To keep blood from clotting in the extracorporeal circuit, anticoagulants are generally used and may cause increased bleeding during the procedure *(i.e., Disseminated Intravascular Coagulopathy)***.
Hemodilution	**Dilution of the patient's blood volume may be caused by the priming of the ECMO circuit.**
Thrombosis/thromboembolism	**Blood clots may form within the extracorporeal circuit due to inadequate blood flow** *(e.g., neurologic injury)***.
Infection	**Defects in the design or construction of the device preventing adequate cleaning and/or sterilization may allow pathogenic organisms to be introduced and may result in infection.**
Mechanical injury to access vessels	**Mechanical injury to vessels may be caused acutely during access, or over time due to the long-term duration of use.**

* Adverse Tissue Reaction = Biocompatibility

** Specific examples of related adverse events provided by September 12, 2013 Panel members

1 Definition modified based on comments received in response to the January 8, 2013 proposed order

2 Mechanical Failure replaces "Loss of Mechanical Integrity" based on comments received in response to the January 8, 2013 proposed order.

3 Definition modified based on comments received in response to the January 8, 2013 proposed order.

The panel will specifically be requested to comment on the risks to health identified by FDA and whether these risks are appropriate for the adult population, and/or whether there are additional risks to health that should be considered for these devices when intended for the adult population.

The Panel will also be asked to discuss the valid scientific evidence presented for the adult population, and whether there is sufficient evidence to establish special controls for the adult pulmonary and/or adult cardiopulmonary patient populations.

Summary of Evidence

Medical Device Report (MDR) Analysis and Recalls

MDR Analysis

The Manufacturer and User Facility Device Experience (MAUDE) database was searched and several analyses were performed by FDA. Due to several limitations related to a MAUDE search for ECMO, the following searches differ by devices and search terms, in an attempt to get the best overall understanding of the device and patient problems that are experienced during long-term extracorporeal oxygenation. One of the biggest limitations includes the fact that ECMO procedures are performed using many cardiopulmonary bypass circuit devices (many of which are used off-label), so searching the MAUDE database using the ECMO product code BYS only (oxygenator for long-term pulmonary support), will not provide an accurate representation of the adverse events experienced with an ECMO circuit.

Historically, the most frequently reported device problems have been related to replacement of the device (20 - 30%) and fluid leaks/leaks (20 - 25%), and the most frequently reported patient problems have been surgery (8 - 13%), and blood loss (7 - 14%).

The following MAUDE searches (4 total) were performed:

DATES: January 1, 2003 through February 25, 2014

SEARCH 1 The membrane lung for long-term pulmonary support defines only an oxygenator. This search was therefore limited to the two product codes used for an oxygenator:

Product Codes: BYS (long-term oxygenator)
DTZ (CPB Oxygenator)

SEARCH 2 Since ECMO is performed with many circuit components, a search was performed that includes all potential ECMO circuit components, and the term "ECMO":

Product Codes: BYS (long-term oxygenator)
DTZ (CPB Oxygenator)
DWF (Cannula)
DTR (heat exchanger)
DTQ (console)
DTM (Arterial filter)
DWB (roller pump)
DWE (tubing)
DTN (reservoir)
KFM (centrifugal pump)

SEARCH 3 A third search was performed to include only ECMO circuit components that have been cleared for long-term use, and the term "ECMO":

Product Codes: BYS (long-term oxygenator)
DTZ (CPB oxygenator)
DWF (cannula)
DTR (heat exchanger)

SEARCH 4 A fourth search was performed to include only ECMO circuit components that have been cleared for long-term use (same product codes as above), and the names of the manufactures of these devices - Scimed, Medtronic, Avalon, Origen, Kendall, Seabrook Medical, and the term "ECMO":

MAUDE Search One

The MAUDE database was searched using the following criteria:
- January 1, 2003 through February 25, 2014
- Product Codes: BYS and DTZ

This MAUDE search yielded a total of 1553 medical device reports (MDRs) including 1356 Manufacturer Reports, 39 Distributor Report, 109 User Facility Reports and 49 Voluntary Reports. Malfunctions were the most frequently reported type of event, with 97 reported deaths (Table 2).

Table 2 Type of Event MAUDE Search One

Report Source	Death	Injury	Malfunction	Other	Invalid	Total
Distributor	8	20	3	0	8	39
Manufacturer	73	163	923	140	57	1356
User Facility	12	17	66	5	9	109
Voluntary	4	21	20	1	3	49
TOTAL	97	221	1012	146	77	1553

**Note: For the September 12, 2013 panel meeting, these search terms were also searched with the term "ECMO", and the result was "0". [January 1, 2003 – June 30, 2013].*

MAUDE Search Two

A second MAUDE search was performed using the following criteria:
- January 1, 2003 through February 25, 2014
- Product Codes: BYS, DTZ, DWF, DTR, DTQ, DTM, DWB, DWE, DTN, KFM; and
- The term "ECMO"

The second MAUDE search yielded a total of 340 MDRs including 224 Manufacturer Reports, 75 User Facility Reports and 35 Voluntary Reports. Malfunctions were the most frequently reported Type of Event, and there were 58 reported deaths (Table 3).

Table 3 Type of Event MAUDE Search Two

Report Source	Death	Injury	Malfunction	Other	Invalid	Total
Distributor	3	1	1	0	1	6
Manufacturer	46	60	104	14	0	224
User Facility	6	5	47	3	14	75
Voluntary	3	17	11	1	3	35
TOTAL	58	83	163	18	18	340

MAUDE Search Three

A third MAUDE search was completed using the following criteria:

- January 1, 2003 through February 25, 2014
- Product Codes: BYS, DTZ, DWF, DTR; and
- The search term “ECMO”.

The third MAUDE search yielded a total of 279 MDRs including 179 Manufacturer Reports, 60 User Facility Reports and 29 Voluntary Reports. Malfunctions were the most frequently reported Type of Event, and 45 reported deaths (Table 4).

Table 4 Type of Event MAUDE Search Three

Report Source	Death	Injury	Malfunction	Other	Invalid	Total
Distributor	4	5	0	0	2	11
Manufacturer	34	52	86	7	0	179
User Facility	4	4	41	3	8	60
Voluntary	3	14	9	1	2	29
TOTAL	**45**	**75**	**136**	**11**	**11**	**279**

MAUDE Search Four

A fourth MAUDE search was performed using the following criteria:

- January 1, 2003 through February 25, 2014
- Product Codes: BYS, DTZ, DWF, DTR;
- Manufacturer names: Scimed, Medtronic, Avalon, Origen, Kendall, Seabrook Medical
- The search term “ECMO”.

The fourth MAUDE search yielded 4 reports associated with Medtronic - however, none of the reports were related to ECMO.

Recalls

The following table (Table 5) represents a list of device recalls for all ECMO circuit components. Since recalls typically reflect design controls or manufacturing issues that would apply regardless of the use of the device, these recalls do not necessarily reflect failures specific to ECMO use (as these circuit components are also used for cardiopulmonary bypass). It should be noted that recalls are classified into a numerical designation (I, II or III) by the FDA to indicate the relative degree of health hazard presented by the product being recalled, with Class I being the most severe.[c] *Note: there has been one additional Class I recall since the September 12, 2013 Panel meeting.*

Table 5 Recalls for ECMO Circuit Devices

Recalls	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
Class I					1				1		1		3
Class II	7	6	6	14	19	11	9	9	16	34	23	2	156
Class III		2	1	2	6	2			2	2			17
Total	**7**	**8**	**7**	**16**	**26**	**13**	**9**	**9**	**19**	**36**	**24**	**2**	**176**

Literature Review

A literature review was conducted for the ECMO 515(i) classification panel that was held on September 12. 2013. The general objective of the literature review for that panel was to evaluate the safety and effectiveness for the use of ECMO in the neonate/infant/pediatric patient populations. The Panel recommended Class II for ECMO in this patient population for specific identified conditions, but also indicated that ECMO use in adults has increased in recent years. They therefore requested that FDA perform a review of the available adult literature, and to consider the results of this review in the context of the overall classification efforts for ECMO.

The literature for the current review is for the use of ECMO among adults for the following indications for use (IFUs):

1) **Veno-Arterial Extracorporeal Membrane Oxygenator (VA-ECMO)**
   a) Indicated for short term support in patients with refractory cardiogenic shock who have an underlying potentially reversible heart condition. For these IFUs, bridge to additional therapy and/or to next decision are possibilities
      i) Failure to Wean (FTW)
      ii) Acute Onset Refractory Cardiogenic Shock unresponsive to Inotropes and/or Intra-Aortic Balloon Pump Counterpulsation (IABP) – chronic or acute cause

[c] Please refer to FDA's website for more information about recalls (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/RecallsCorrectionsAndRemovals/default.htm)

b) Salvage
   i) Extracorporeal Cardiopulmonary Resuscitation (ECPR)

c) Pulmonary blood flow acutely/chronically impeded (not a parenchymal problem)
   i) Massive or Saddle Pulmonary emboli
   ii) Primary Pulmonary Hypertension

d) Pulmonary parenchymal disease
   i) Acute infections of unknown etiologies in patients for whom gas exchange is inadequate and the function of the right heart is sufficiently compromised to warrant veno-arterial (as opposed to veno-venous) ECMO as a first-line therapy

2) Veno-Venous Extracorporeal Membrane Oxygenator (VV-ECMO)

a) Indicated to provide oxygenation and rest to the lungs, decreasing the insult caused by mechanical ventilation. For these IFUs, bridge-to-lung transplant or weaning are possibilities
   i) Chronic Obstructive Pulmonary Disease (COPD)
   ii) ARDS (Acute Respiratory Distress Syndrome)
   iii) Influenza A (H1N1)
   iv) Flu, influenza, or pneumonia
   v) Graft dysfunction after lung transplantation

Methodology

Figure 2 presents the diagram of article retrieval and selection. In summary, 700 articles were identified from PubMed and, after reviewing their abstracts, 490 were excluded. The main reasons for excluding articles were: case reports (n=146), studies with ≤10 patients (n=105), and were conducted before 2000 (n=81).

The full-texts of the remaining 210 articles were examined for eligibility, of which 182 were excluded. The main reasons for excluding these articles were: age <18 years (n=44), studies conducted before 2000 (n=30), studies with ≤10 patients (n=23), and the studies did not provide results for ECMO or IFUs (n=17). Thus, 28 full-text articles remained for detailed assessment in this review.[2-29] Tables 6, 8, and Appendix B present the results by IFU and some studies are included in the tables more than once given that they had results for more than one IFU. No studies evaluating the use of ECMO for massive or saddle pulmonary emboli, primary pulmonary hypertension, pulmonary parenchymal disease, and COPD were identified.

Two of the studies included in the literature review used data from the international registry of the Extracorporeal Life Support Organization (ELSO).[17,27] The ELSO registry captured the majority of ECMO cases performed in the United States.[17] In 2011, ELSO had 170 domestic and international centers actively reporting data to the registry. Two additional studies were conducted in the United States[8,24] and the rest were conducted in Europe and Asia. The study designs from these studies included one meta-analysis, one randomized clinical trial (RCT), two cohorts, one case-control, and the rest were case series (Table 6). Although the results from one RCT[20] and two cohorts[15,21] were also used in the meta-analysis,[29] additional results from these studies are presented in Appendix B.

Figure 2. Flow diagram of article retrieval and selection

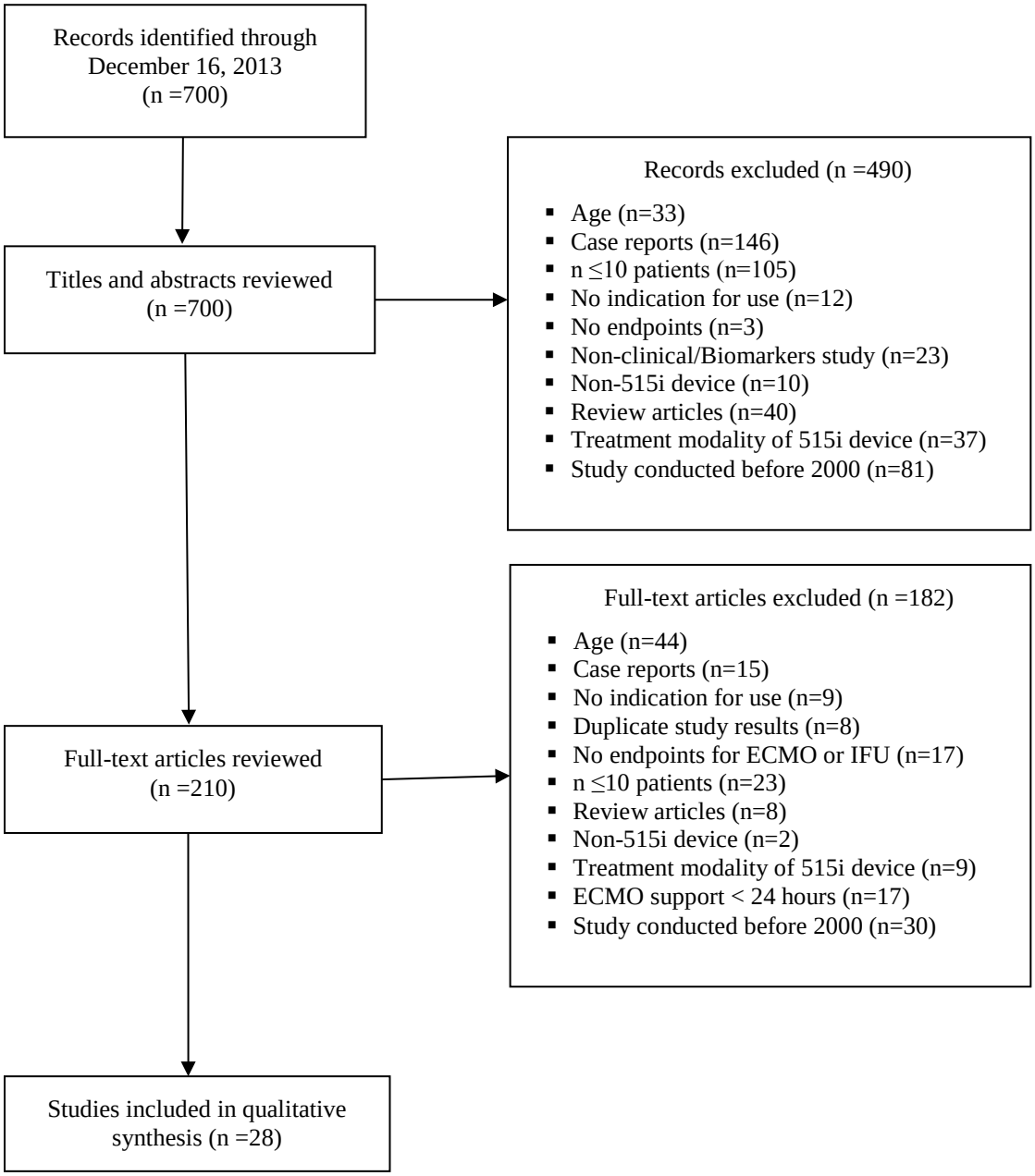


Table 6- Study design of all publications included within this report

Author (Year)	Study Design	Study Location
Veno-Arterial Extracorporeal Membrane Oxygenator (VA-ECMO)		
Failure to Wean (FTW)		
Loforte, 2012[12]	Case Series	Italy
Acute Onset Refractory Cardiogenic Shock		
Aissaoui, 2011[2]	Case Series	France
Bakhtiary, 2008[3]	Case Series	Germany
Barth, 2012[4]	Case Series	France
Bréchot, 2013[5]	Case Series	France
Hsu, 2010[10]	Case Series	Taiwan
Loforte, 2012[12]	Case Series	Italy
Luo, 2009[13]	Case Series	China
Sakamoto, 2012[22]	Case Series	Japan
Schmidt, 2012[23]	Case Series	France
Wang, 2009[28]	Case Series	China
Extracorporeal Cardiopulmonary Resuscitation (ECPR)		
Sakamoto, 2012[22]	Case Series	Japan
Schmidt, 2012[23]	Case Series	France
Shin, 2011[25]	Case-Control Study	South Korea
Thiagarajan, 2009[27]	Case Series/ELSO Registry	International
Veno-Venous Extracorporeal Membrane Oxygenator (VV-ECMO)		
Acute Respiratory Distress Syndrome (ARDS)		
Haneya, 2012[7]	Case Series	Germany
Linden, 2009[11]	Case Series	Sweden
Müller, 2009[14]	Case Series	Germany
Noah, 2013[16]	Case Series	United Kingdom
Patroniti, 2011[19]	Case Series	Italy
Peek, 2009[20]*	Randomized Clinical Trial	United Kingdom
Zampieri, 2013[29]	Meta-analysis	United Kingdom and France
Influenza A (H1N1)		
Chenaitia, 2011[6]	Case Series	France
Holzgraefe , 2010[9]	Case Series	Sweden
Noah, 2011[15]*	Cohort	United Kingdom
Paden, 2013[17]	Case Series/ELSO Registry	International
Patroniti, 2011[19]	Case Series	Italy
Pham, 2012[21]*	Cohort	France
Takeda, 2012[26]	Case Series	Japan
Pneumonia		
Park, 2012[18]	Case-Series	South Korea
Graft dysfunction after lung transplantation		
Hartwig, 2012[8]	Case Series	United States
Shafii, 2012[24]	Case Series	United States

Abbreviation: ELSO: Extracorporeal Life Support Organization. *Studies included in Zampieri, 2013.

Veno-Arterial Extracorporeal Membrane Oxygenator (VA-ECMO)

Failure to Wean (FTW)

This review identified one case series study evaluating the survival of adults that had ECMO support due to failure to wean from cardiopulmonary bypass.[12] This study reported a 38% survival to hospital discharge among 50 patients with postcardiotomy shock (Appendix B). One patient was bridged to a Left Ventricular Assist Device (LVAD) and survived to hospital discharge after 311 days of ongoing support.

Acute Onset Refractory Cardiogenic Shock

Ten case series studies assessed ECMO use for acute onset Refractory Cardiogenic Shock (RCS).[2-5,10,12,13,22,23,28] Survival to hospital discharge among these studies ranged from 24% (9/38) in a study of German patients[3] to 71% (10/14) in a study of patients with RCS due to bacterial septic shock[5] (Appendix B). Survival to one year or more was reported in three studies.[3,10,29] In a study conducted among 51 patients from Taiwan, 33% and 29% of the patients were alive at discharge and at one year, respectively.[10] Bakhtiary[3] reported the lowest survival to discharge among the studies identified for this IFU with a 29% survival to discharge (including 3 bridged to LVAD and one heart transplant) and at three years the survival decreased to 22% with the death of three patients. Wang et al. evaluated the survival and quality of life measures in 62 patients with RCS and supported with ECMO in China[28]. In this study, survival rates to hospital discharge and at four years follow-up were 55% (34/62) and 52% (32/62), respectively. Quality of life outcomes from these patients were evaluated at four years follow-up and compared to a random sample of 85 out of 12,644 cardiac surgery patients treated during the same study time period and who did not receive ECMO. The mean scores after cardiac surgery were similar for the ECMO survivors and the patients who did not receive ECMO support, except that the vitality and mental health scores were lower among the ECMO survivors ($p<0.05$).[28]

Appendix B presents the major causes of deaths reported in the studies, which included multiple organ failure (MOF), including due to sepsis; neurological damage owing to cardiac arrest; heart failure, and pulmonary infections. The complications most commonly reported among these studies included renal failure (31-87%), infections (6-65%), bleeding (13-51%), the need for rethoracotomy (16-87%), the need for blood transfusion (100%), haematuria (33%), pulmonary complications (14-22%), and liver failure (41%) (Appendix B). The most common ECMO circuit complications reported was change of oxygenator.[3,13,28] The change of the oxygenator is considered a complication. The oxygenator needs to be changed when it starts to fail and this is usually due to a leak in the membrane or wetting such that gas exchange is affected.

Extracorporeal Cardiopulmonary Resuscitation (ECPR)

Four studies were identified that examined ECMO used for Cardiopulmonary Resuscitation (ECPR) among adults.[22,23,25,27] Survival to discharge ranged from 19%[27] to 56%[22] (Appendix B). A case-control study evaluated 60 matched patients from South Korea and reported statistically significant differences in the survival among patients that received ECPR and those that received CPR.[25] These differences in survival among ECPR recipients compared to CPR recipients were observed for both, in-hospital (31.7% vs. 10%, $p<0.05$) and at six months (31.7% vs. 8.3%, $p<0.05$). The proportion of patients without neurologic impairment (Cerebral Performance Categories score ≤ 2) among ECPR recipients was higher compared to CPR recipients both in-hospital (23.3% vs. 5%, $p<0.05$) and at six months (also 23.3% vs. 5%, $p<0.05$). The 6-month

hazard ratio of mortality or significant neurologic impairment for ECPR recipients was half that of CPR recipients after adjusting for relevant baseline clinical characteristics and CPR variables (95% CI 0.30-0.84).[25]

The ELSO registry is a registry of ECMO cases from 170 centers from the United States and international as of 2011.[17] In a study using ELSO data from nearly 300 patients that received ECPR, survival to hospital discharge for the 1992-2007 period was 27%.[27] Survival for the 2000-2003 period was higher compared to any of the other time periods (Table 7). The study did not provide reasons for the increase in survival to hospital discharge seen in 2000-2003. Overall, ninety-eight (33%) patients suffered neurologic complications with the most common being brain death (21%). The incidence of brain death was highest in the recent years 2004-2007 (26%) compared to 1992-1999 (16%) and 2000-2003 (13%; $p<0.03$).

Table 7. Survival to hospital discharge*

	Survived	*Total*	*Percentage (95% CI)*
1992–1995	1	4	25 (5 – 70)
1996–1999	6	27	22 (11 – 41)
2000–2003	41	101	41 (32 – 50)
2004–2007	31	163	19 (14 – 26)

**Calculated from the study data*[28].

Veno-Venous Extracorporeal Membrane Oxygenator (VV-ECMO)

Acute Respiratory Distress Syndrome (ARDS)

Seven articles were identified with relevant data on the use of ECMO for ARDS in adults: one meta-analysis[29], one RCT[20], and five case series[7,11,14,16,19]. Survival to discharge ranged from 45%[14] to 84%[16] (Appendix B).

Zampieri[29] conducted a meta-analysis of one RCT[20] and two cohort studies[15,21]. Regarding the types of ARDS, 60% of the RCT participants suffered pneumonia-attributed ARDS and both cohort studies reported on H1N1 ARDS exclusively. The RCT[20] and one of the cohort studies[16] conducted their primary analysis by intention-to-treat. The meta-analysis excluded patients that did not received ECMO as a treatment; therefore, a total of 179 ECMO and 174 non-ECMO patients were available in the pooled analysis. The odds ratio (OR) for in-hospital mortality was 0.71 (95% CI 0.34-1.47) for ECMO patients when compared to non-ECMO patients. This pooled OR was obtained from the results of the cohort analyses using propensity scores (PS) and matching ECMO and non-ECMO patients without replacement (a matched non-ECMO patient cannot be used for matching another ECMO patient). The pooled OR was 0.52 (95% CI 0.35 - 0.76) when estimated using PS with replacement.

In the meta-analysis, Zampieri et al[29] presented the observed and expected mortality of case series of severe ARDS patients that received ECMO which they calculated using Simplified Acute Physiology Score (SAPS) II, SAPS III, Acute Physiology and Chronic Health Evaluation (APACHE) II, or lung injury score (Figure 3). Note that the meta-analysis only used 3 studies, A RCT from Peek et al.[20] and two cohort studies from Noah et al.[16] and Pham et al.[22]; the other studies presented in the figure are exclusively the case series not included in the meta-analysis. The results of the case series show a reduction in mortality, compared to the expected mortality if no treatment is provided, in nearly all of the studies.

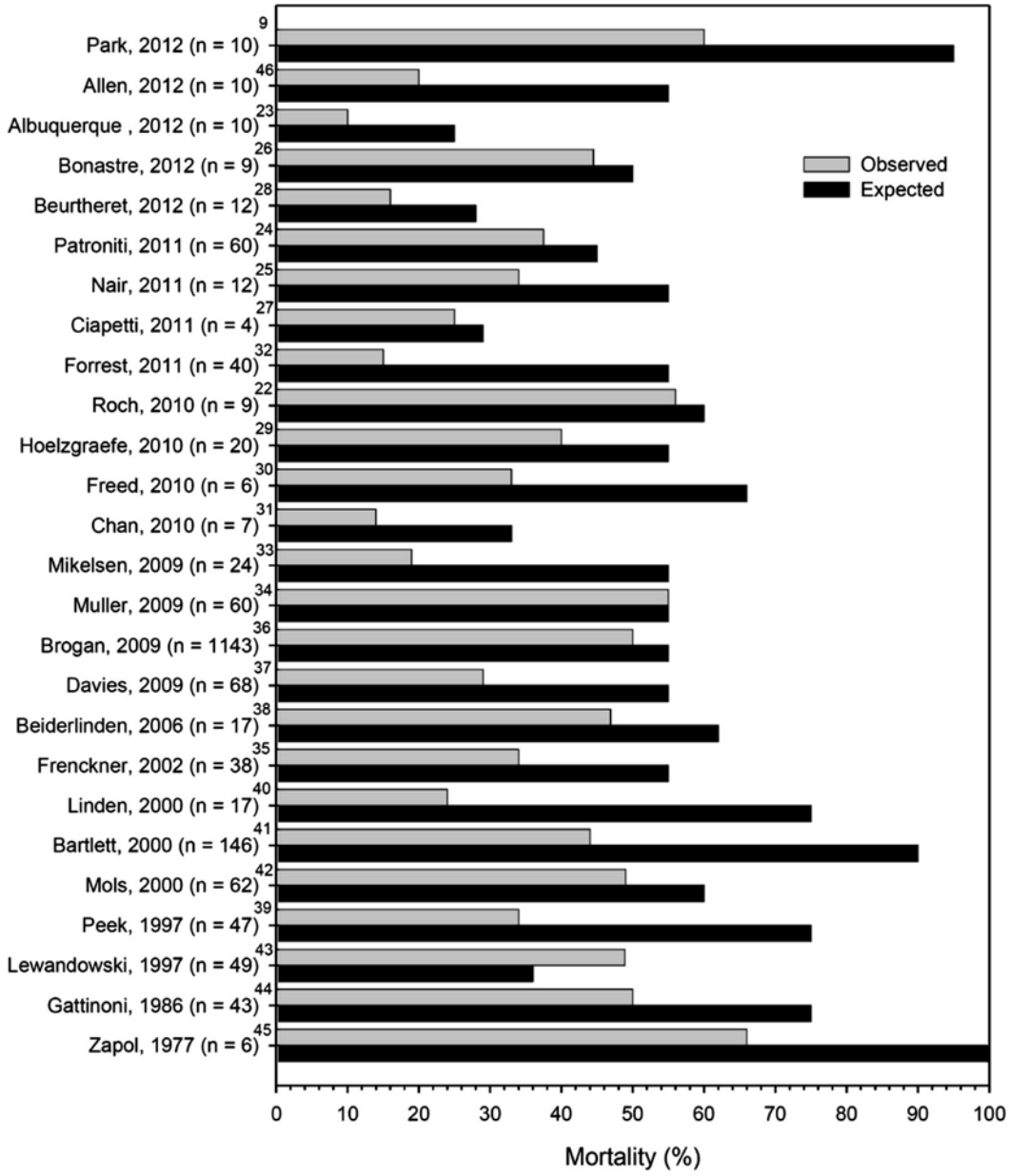


Figure 3. Expected and observed mortality of case series of severe respiratory failure patients supported with ECMO. *Expected mortality was estimated using Simplified Acute Physiology Score (SAPS) II, SAPS III, Acute Physiology and Chronic Health Evaluation (APACHE) II, or lung injury score. Source: Zampieri et al.*[29]

The Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure (CESAR) RCT was conducted among 180 patients in the United Kingdom.[20] Out of the 90 patients that were randomly allocated to ECMO, 75% actually received ECMO treatment. Six-month survival without disability was higher among ECMO-allocated patients (57/90 [63%]) compared to those that received conventional ventilatory support (41/87 [47%]). ECMO-allocated patients had a 30% lower risk of dying or being severely disabled at six months (Relative Risk [RR] 0.69; 95% CI 0.5 - 0.97). The major causes of death among both treatment groups were MOF and respiratory failure.

Linden et al.[11] evaluated the survival to hospital discharge and after discharge of 37 ECMO patients. Twenty-six (70%) survived to hospital discharge and 57% (21/37) post-discharge (range of months to follow-up: 12 to 50). Out of the 21 post-discharge survivors, 16 (76%) reported that they were able to return to the same occupation as before ECMO, two (9.5%) had retired, two (9.5%) on disability and one (5%) was receiving medical rehabilitation. All patients were living at home and none were in need of oxygen support. While most patients reported reduced health related quality of life, the authors reported that respiratory symptoms were less than conventionally treated ARDS patients in previous studies.

Miniaturized ECMO, a smaller sized portable ECMO, was evaluated by Müller[14] and Haneya.[7] Survival to discharge was 68.2% for Haneya[7] and 45% for Müller.[14] Sepsis-related MOF was the leading cause of mortality in both studies. Device exchange because of circuit thrombus formation was needed in 41% of Haneya's cases.[7] Surgical site bleeding and thrombosis of oxygenator were seen in 18% and 17% of Müller[14] patients, respectively.

Influenza A (H1N1)

ECMO use for the treatment of ARDS due to H1N1 infection in adults was identified in two cohorts,[15,21] one case series with data from the ELSO registry,[17] and an additional four case series studies[6,9,19,26](Appendix B). For these studies, survival to hospital discharge ranged from 36% to 92% for ARDS due to H1N1 (Appendix B). Data from the two cohort studies[15,21] were included in Zampieri et al.'s meta-analysis[29] with additional results presented in this section.

Paden et al.[17] reported 67% survival to hospital discharge among 237 H1N1-infected adults included in the ELSO registry during August 2009 - March 2010. Noah et al. and Pham et al.'s cohort studies and an Italian case series study of 49 patients reported comparable survival rates ranging from 50% to 76%.[15,19,21]

Five of the studies[9,15,19,21,26] presented results on the major causes of death and/or patients' complication including those related to the ECMO circuit (Appendix B). The most common major causes of death reported in these studies were MOF, cerebral hemorrhage, refractory hypoxemia, refractory shock, septic shock, acute renal failure, and infection (Appendix B). Two studies (one cohort[21] and one case series[9]) reported one or more ECMO-related complications among 53% (65/123) and 62% (8/13), respectively. The most common complications observed among all of the studies identified for ECMO use in ARDS due to H1N1 infection were disseminated intravascular coagulation (71%), massive bleeding (57%), epistaxis (12%), and cannulation-site bleeding (8% - 14%). Commonly reported ECMO circuit complication included cannula-site infection and/or septicemia (11%), cannulation complications (21%), oxygenator failures (58%), and blood clots (29%) (Appendix B).

Pneumonia

One case series study from South Korea[18] evaluated the use of ECMO among patients with respiratory failure due to pneumonia. Park et al.[18] observed a 33% (4/12) survival to hospital discharge and also at one year among 12 liver transplant patients that were placed on ECMO due to pneumonia. In this study, the major cause of death in this study was MOF due to sepsis.

Graft dysfunction after lung transplantation

Two case series studies, both conducted among US patients that required ECMO for severe primary graft dysfunction after lung transplantation, were identified for this indication.[8, 24] Hartwig et al. reported survival rates at 30 days, one year, and 5 years were 82%, 64%, and 49%, respectively, among 28 transplants.[8] Blood stream infections at 90 days were observed in 36% (10) of the patients in this study. Freedom from bronchiolitis obliterans syndrome was 88% at 3 years. Shafii et al[24] studied 13 usual interstitial pneumonia patients that were placed on ECMO (62% on VV-ECMO) with the intent to use it as a bridge-to-transplant (BTT). A total of 9 (69%) patients, all receiving double lung transplant, survived. The rest of the patients died before transplant (2) or after double (1) or single (1) lung transplant.

Table 8 Summary of Evidence by Indication for Use

Indication for Use	*Number of articles*	*Types of studies*	*Sample Size (range)*	*Survival to Discharge (%)*
Veno-Arterial (VA) ECMO				
Failure to Wean	1	Case Series	50	38
Acute Onset Refractory Cardiogenic Shock	10	Case Series	14 - 242	24 - 71
ECMO Cardiopulmonary Resuscitation	4	Case-Control and Case Series	28 - 85	19 - 56
Massive or Saddle Pulmonary Emboli	0			
Primary Pulmonary Hypertension	0			
Pulmonary Parenchymal Disease	0			
Veno-Venous (VV) ECMO				
Chronic Obstructive Pulmonary Disease (COPD)	0			
Acute Respiratory Distress Syndrome (ARDS)	7	Meta-Analysis, RCT, and Case Series	11 - 90	45 - 84
Influenza A (H1N1)	7	Cohort and Case Series	11 - 237	36 - 92
Pneumonia	1	Case Series	12	36
Graft Dysfunction after Lung Transplantation	2	Case Series	13 - 28	69- 82

Assessment

This review of the literature was conducted to evaluate whether a reasonable assurance of safety and effectiveness for the use of ECMO among adults can be demonstrated with valid scientific evidence. The literature search restricted ECMO as a MeSH major topic and narrowed to the MeSH terms available for IFUs, age, human studies, and published in English (Appendix C). Although this approach is more efficient as it increases the specificity of the studies to evaluate, the loss of sensitivity can result in missed studies. In PubMed, MeSH terms identify those articles that have been classified to be relevant to the topic included in the term but there is a lag between the availability of articles and the time these articles are indexed with MeSH terms; therefore, using MeSH term will not include those articles that have been recently published. To minimize not capturing recent articles, the date of the last article indexed, at the time of the search, in PubMed was identified. Articles without "MEDLINE" status (i.e. not indexed) were included for review. Out of the 28 articles identified, only two (7%) were conducted among patients from the United States[8,24] (Table 6).

No studies evaluating the use of ECMO were available for massive or saddle pulmonary emboli, primary pulmonary hypertension, pulmonary parenchymal disease, and COPD (Table 8). For a number of specific indications only case series were identified (failure to wean (1), acute onset refractory cardiogenic shock (10), and graft dysfunction after lung transplantation (1)) (Table 8). Case series studies do not have comparison groups. Not having a comparison group limits the interpretation of the results as data on survival and complications related to ECMO use cannot be attributable to the actual use of the device vs. the patient population, who already are at high risk for death due to other complications.

Acute Onset Refractory Cardiogenic Shock had the most studies identified; however, all of these were case series. ARDS and ARDS due to H1N1 infection had the second largest number of studies identified, including a meta-analysis of three outside of the United States (OUS) studies, the CESAR trial with ARDS and two cohorts of patients with ARDS from H1N1 infection.

The results of the Zampieri[29] meta-analysis showed that ECMO-patients with ARDS with or without H1N1 infection had lower odds of dying in the hospital compared to non-ECMO patients, although this result was not statistically significant and a rather imprecise estimate. However, if the analysis was done using alternative severity-matching methods, which increased the sample size, the results showed a statistically significant decrease in mortality in favor of ECMO. This decrease in the OR and reaching statistical significance was probably driven by Pham et al.'s cohort study[21] in which the ORs changed directions, from an increase in the odds of mortality when the ECMO patients were matched without replacement (OR 1.48; 95% CI 0.68 - 3.21) to a decrease (OR 0.45; 95% CI 0.25–0.78) if matching with replacement was used. The reason for this difference may be that the initially unmatched-ECMO patients in the cohort were

younger and, although they had more severe respiratory failure, they had half the mortality than the ECMO patients that found a match. When analysis with replacement was used, these initially unmatched-ECMO patients were now matched with the same severe non-ECMO patients and this may have artificially shown a better survival among the ECMO patients.

The CESAR trial[20] is the only RCT conducted to evaluate the use of ECMO on patients with ARDS using contemporary ECMO circuits and showed results in favor of ECMO treatment; however, limitations of this trial are that a large percentage (25%) of the ECMO-allocated patients did not received the treatment and the treatment for the comparison group, conventional management with mechanical ventilation, was not standardized across the sites.

Noah et al.'s results[16] of the cohort study among H1N1-infected patients are more robust. The results continue to favor ECMO, the decrease in the risk of in-hospital mortality ranged from 40% to 60% and remained statistically significant, independently of the matching technique used or restricting the analysis to only patients that received ECMO (the main analysis was among ECMO-referred patients).

Most of the studies used the appropriate ECMO mode (VV or VA) for the relevant IFU; however, there was limited information on ECMO implementation in patients within the same study. Although the ELSO registry has guidelines for ECMO patient selection, technique, and timing of initiation, there may still be variability in the implementation of these guidelines[17]. Overall, all of the patients should have "acute, potentially reversible cardiorespiratory failure in which conventional support has been deemed inadequate and the patient faces a predicted risk of mortality greater than 50%."[17]

Clinical Evidence

Clinical rationale for ECMO

There are two types of ECMO – venoarterial (VA) and venovenous (VV). Both provide respiratory support, but only VA ECMO provides hemodynamic support. In general, ECMO has been used in clinical situations where there is primary or secondary failure of the lungs and/or heart to provide physiologic function compatible with maintenance of life. In these clinical situations, death is imminent unless effective medical and/or mechanical interventions are successful in immediately reversing the underlying cause or supporting the affected organ functions until normal reparative processes take hold or proven alternative life-saving therapies can be initiated.

It is not the intent of FDA to restrict the practice of medicine with regard to use of available marketed devices in situations where no other proven therapeutic alternative is available, death without intervention is unavoidable, and the rationale for use is plausible.

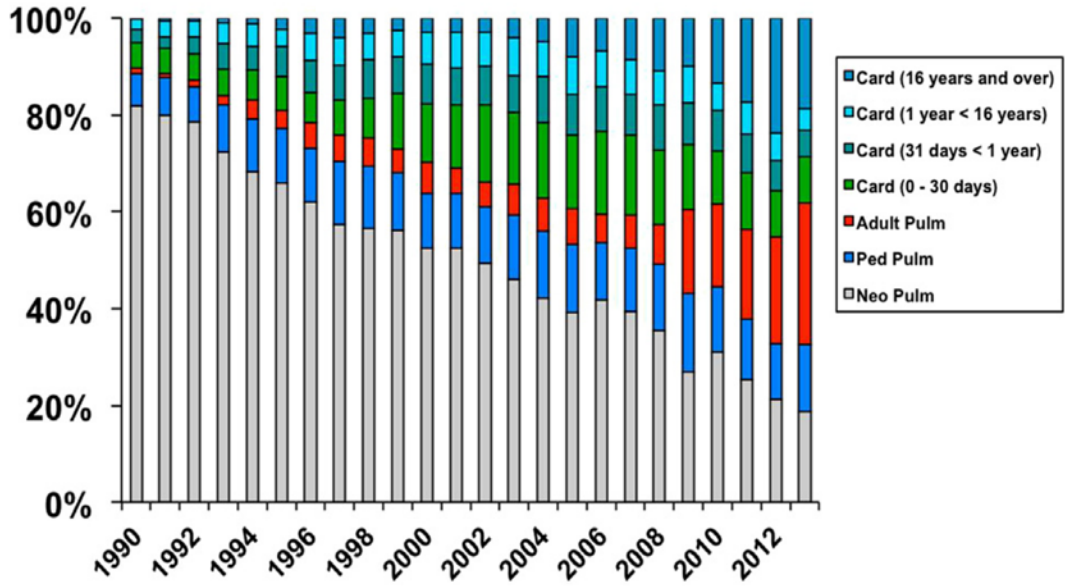
Respiratory

ECMO is typically used as a rescue therapy, instituted in adult respiratory failure only after all other reasonable avenues of appropriate medical therapy have been exhausted. Medical therapy may include not only improved mechanical lung protective ventilation strategies, but also inhalation agents and pharmacologic measures aimed at reducing pulmonary vascular resistance as well as prone positioning to optimize lung recruitment with minimization of atelectasis.

Cardiopulmonary

In the case of cardiopulmonary failure ECMO is typically used in the post cardiotomy or post CPR settings where there is failure to wean off cardiopulmonary bypass or failure to effectively restore cardiac function following prolonged resuscitative efforts. In these settings where the onset of cardiogenic shock is acute and catastrophic, pharmacologic and/or mechanical ventricular assist therapies have failed (or are unavailable on site), and significant concomitant pulmonary dysfunction is suspected or evident. In these specific circumstances, death is imminent and all other therapeutic modalities have been exhausted.

Figure 4: Evolving Yearly Distribution of Cases Reported to the Extracorporeal Life Support (ELSO) Registry: 1990-2013[d]



[d] Bartlett RH. Jour Amer Coll Surgeons 2014;218:317-327

For the purposes of this Panel Summary, we will divide major patterns of ECMO use in adults into two broad categories: Cardiopulmonary Failure (cardiogenic shock and heart failure) and Pulmonary Failure. Although there are certainly abundant examples of bi-organ system failure, the underlying cause resulting in need for either cardiac and/or respiratory ECMO support usually can be attributed to a primary origin of either the heart (i.e., acute catastrophic loss of pump function) or the lungs (i.e., progressive loss in ability to provide adequate gas exchange due to parenchymal, airway, chest wall or pulmonary blood flow abnormalities).

Clinical Indications – Cardiopulmonary Failure

Note: Use of devices such as percutaneous or durable VADs to provide temporary or prolonged mechanical ventricular support for the prevention and/or treatment of acute or chronic heart failure requires a pre-market approval (PMA) application for approval and are not the subject of this classification discussion.

Cardiogenic Shock/Heart Failure

For cardiogenic shock and heart failure, standard of care therapies are directed at the underlying cause. Depending on the underlying cause and the mode and rapidity of onset, therapy may include a multitude of combinations of standard therapies. Examples of standard of care therapies for cardiogenic shock include a wide range of cause or effect directed treatments such as pharmacologic interventions with antiarrhythmic, chronotropic, inotropic or vasoactive drugs; cardiopulmonary resuscitation (CPR) and/or cardioversion; intravascular mechanical support using an intra-aortic balloon pump (IABP); interventional procedures for restoration of coronary blood flow or relief of valvular stenosis or insufficiency; urgent or emergent surgery; intraoperative extension of cardiopulmonary bypass or performance of additional cardiac procedures (e.g., additional coronary bypass graft or valve procedure following planned surgery) following surgery.

All of these measures have proven benefit and make therapeutic sense for reversal or palliation of the underlying cause or for interruption or reversal of the causal chain of events. However, when these etiology or physiology based standard of care treatments and interventions fail or are exhausted, no other therapeutic modalities remain. Without restoration or augmentation of cardiac or cardiopulmonary function by mechanical artificial means such as insertion of temporary percutaneous ventricular assist devices (VADs), implantable durable VADs or ECMO, death is an unavoidable outcome.

For the purposes of this discussion, FDA has organized cardiogenic shock/heart failure into 3 primary categories (Figure 4) based on the appropriate therapeutic modes of cardiopulmonary or ventricular support required for therapy:

- Acute Catastrophic Cardiogenic Shock (CS)
- Sub-Acute CS or Heart Failure (HF)
- Chronic Progressive HF

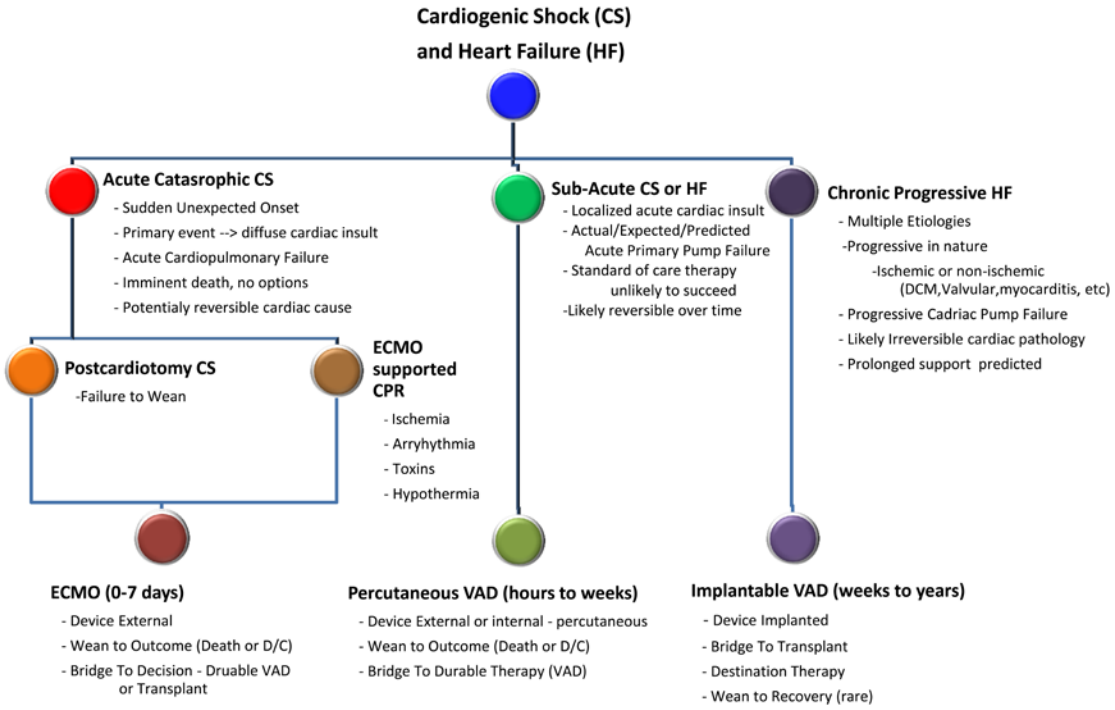


Figure 5: Categories of Cardiogenic Shock and Heart Failure relative to appropriate modes of Mechanical Support

ECMO has been used historically in the setting of **acute catastrophic cardiogenic shock** with primary cardiac causes. These are characterized by sudden unexpected primary cardiac events which are catastrophic in nature. The underlying cardiac injury, which may or may not be reversible, typically results in a diffuse global cardiac injury (i.e., acute loss of pump function) and secondary acute pulmonary failure (i.e., acute cardiopulmonary failure) due to a lack of forward flow through the lungs, pulmonary edema, or a combination of the two. The typically diffuse nature of global cardiac injury may be temporary (e.g., myocardial stunning) or permanent (e.g., local or diffuse sub-endocardial or full thickness myocardial infarction). In these often uncontrolled settings, **death is imminent** and immediate treatment directed at stabilization of both organ systems is indicated with later determination of the specific needs for each system as the

patient's condition stabilizes. The two particular circumstances where ECMO is used clinically as salvage therapy for treatment of acute catastrophic cardiogenic shock resulting in acute cardiopulmonary failure are:

- Failure of prolonged cardiopulmonary resuscitation (CPR), and
- Post-cardiotomy Failure to Wean (FTW) from cardiopulmonary bypass.

Ultimately, the reversibility and time needed for reversal of the underlying diffuse cardiac injury (determinants of duration of ECMO), and the functional preservation of other critical organ systems (e.g., immune, renal and neurological) while on ECMO are the prime determinants of outcomes which include death, wean to discharge or wean to other therapy (bridge to decision).

Generally, primary cardiac failure which is **sub-acute or chronic progressive** in nature results in primary heart failure which is treated under more controlled circumstances using various combinations of the therapeutic modalities summarized above. In these sub-acute or chronic progressive and generally non-catastrophic settings, right and/or left heart failure is predominant and pulmonary function may be acutely or chronically compromised as a secondary effect. However the degree of pulmonary dysfunction present is treatable with standard ventilator and/or pharmacologic measures aimed at optimizing pulmonary function and hemodynamics. With the availability of other therapeutic options including percutaneous and durable VADS and organ transplantation as a primary or secondary therapy, ECMO therapy is usually not utilized in these patients in the absence of acute and unpredicted clinical decompensation (acute cardiogenic shock) which catastrophically affects both organ systems.
Acute Catastrophic Cardiogenic Shock

Postcardiotomy Failure to Wean

The need for postcardiotomy mechanical support is uncommon, with an incidence of 0.5 - 1%.[e] Risk factors for development of postcardiotomy CS requiring ECMO in their Cleveland Clinic experience is typical (97 patients; Operated on September 1992 - January 2000) and are summarized in the table below:

Table 9 Risk Factors for ECMO[d]

[e] Smediera,NG and Blackstone EH. Postcardiotomy Mechanical Support: Risk Factors and Outcomes. Ann Thorac Surg 2001;71:S60–6

Table 3. Risk Factors for Extracorporeal Membrane Oxygenation

Factor	Logistic Coefficient ± SD	*p*	Reliability[a] (%)
Demography			
Young age[b]	−0.81 ± 0.190	<0.0001	98
Clinical status			
More cardiac reoperations[c]	1.82 ± 0.22	<0.0001	99.8
Emergency operation	2.4 ± 0.24	<0.0001	100
Higher creatinine	0.197 ± 0.050	<0.0001	66
Cardiac comorbidity			
Left main disease (≥50% diameter stenosis)	0.78 ± 0.24	0.001	75
Greater LV dysfunction[d]	0.044 ± 0.0157	0.005	66
History of previous MI	0.56 ± 0.23	0.02	54
Experience			
More recent date of operation[e]	0.36 ± 0.140	0.009	89
Intercept	−6.33		
Goodness-of-fit (c)	0.83		

[a] Percent of times that variable appeared in 500 bootstrap resamplings. [b] [age/50]^2 squared transformation. [c] ln[surgery number^{-1}]natural logarithmic transformation. [d] exp[LV dysfunction grade (1 = none, 2 = mild, 3 = moderate, 4 = severe)] exponential transformation. [e] ln[years since September 1, 1992] natural logarithmic transformation.

LV = left ventricular; MI = myocardial infarction.

Other unmeasurable factors may include factors such as the adequacy or effectiveness of myocardial protection and cardiopulmonary bypass, and the conduct, adequacy or appropriateness of surgery.

In adults, ECMO for postcardiotomy failure to wean may be instituted either as primary therapy following failed optimal medical therapy and IABP, or following failed attempts of percutaneous (temporary) VAD therapy which are unsuccessful due to the presence of severe secondary pulmonary failure and/or severe biventricular failure.

Over the last decade, extracorporeal life support (ECLS) in the cardiac population is responsible for the majority of the growth of ECLS use. The distribution of cardiac related ECLS patients by age and indication from data reported to the ELSO registry is shown in **Table 10** below (1990-2013). The majority of this use (57% total, 72% of patients >16 years old) has been in the peri-operative period surrounding correction of congenital cardiac defects. Medical cardiac disease including myocarditis (67% survival) and cardiomyopathy (56% survival) have the best overall survival which is significantly greater than the congenital cardiac defect group ($p < 0.0001$).

Table 10: Cumulative Indications for Cardiac Related ECMO by age as Reported to ELSO Registry: 1990-2013[f]

[f] Paden ML et al. Seminars in Perinatolgy 2014; 39:65-70

	Total runs	Number surviving	% Surviving
0–30 Days			
Congenital defect	4694	1816	39
Cardiogenic shock	77	29	38
Cardiomyopathy	121	73	60
Myocarditis	66	33	50
Other	487	211	43
31 Days and <1 year			
Congenital defect	2725	1232	45
Cardiogenic shock	47	18	38
Cardiomyopathy	169	94	56
Myocarditis	80	59	74
Other	480	239	50
1 Year and <16 years			
Congenital defect	1341	629	47
Cardiogenic shock	105	55	52
Cardiomyopathy	473	291	62
Myocarditis	241	169	70
Other	729	395	54
>16 Years			
Congenital defect	239	79	33
Cardiogenic shock	549	201	37
Cardiomyopathy	372	181	49
Myocarditis	123	82	67
Other	2243	874	39

Results of ECMO for these postcardiotomy cardiogenic shock (PCS) indications have been extensively reported in both pediatric and adult populations. Regardless of the underlying cardiac insult, relatively consistent survival results for adult and pediatric ECMO have been reported. In general for acute catastrophic cardiogenic shock, it can be expected that approximately 50-70% of patients will wean from ECMO, and 35-50% will be discharged alive.[g] Disparate results between individual centers are expected due to differences in patient mix and indications, varying thresholds for the decision to institute ECMO, and varying experience in the care of patients requiring ECMO both while on support and post weaning. A meta-analysis by Cheng et al. reported survival to discharge data from numerous series of adult patients undergoing ECMO for postcardiotomy cardiogenic shock (PCS) and cardiac arrest indications[g]: (Table 11)

Table 11 Meta-analysis Discharge data for ECMO (PCS and Cardiac Arrest)

[g] Cheng R et al. Ann Thorac Surg 2014;97:610–6

Table 1. Studies Included in Analysis: Baseline Characteristics

Study	Number of Patients	Patient Type	Average Age (y)	Age Range (y)	Males (%)	Peripheral ECMO (n, %)	IABP (n, %)	Average Time on ECMO (h)	Survival to D/C (n, %)	Bridged to VAD (n, %)/Survival to D/C (n, %)	Bridged to HTP (n, %)/Survival to D/C (n, %)
Bakhtiary et al [1]	45	PCCS	60.1 ± 13.6	Adults	78	29 (64)	30 (67)	153.6	13 (28.9)	5 (11.1)/3 (60)	2 (4.4)/1 (50)
Belle et al [20]	51	Mixed	51 ± 15	≥18	75	51 (100)	5 (10)	–	14 (27.5)	–	–
Bermudez et al [9]	42	Mixed	53.5	28–80	83	37 (88)	37 (88)	67.1	–	22 (52.4)/–	–
Elsharkawy et al [2]	233	PCCS	57	Adults	67	156 (67)	22 (9.4)	–	84 (36.1)	–	–
Hei et al [19]	68	PCCS	49.2 ± 13.3	≥18	76	67 (99)	11 (16)	114.6	43 (63.2)	–	8 (11.8)/6 (75)
Hsu et al [3]	51	PCCS	63 ± 15.7	Adults	71	51 (100)	–	180	17 (33.3)	–	3 (5.9)/3 (100)
Kagawa et al [21]	77	CA	61.9	18–74	71	77 (100)	52 (68)	–	16 (20.8)	4 (5.2)/–	–
Kim et al [10]	27	AMI	63.7 ± 11	45–81	59	27 (100)	2 (7)	30.2	16 (59.3)	–	–
Loforte et al [17]	73	Mixed	60.3 ± 11.6	23–84	75	73 (100)	73 (100)	261.6	33 (45.2)	3 (4.1)/2 (66.7)	0 (0)/N/A
Moraca et al [22]	26	Mixed	57	18–76	69	24 (92)	21 (80)	72	17 (65.4)	9 (34.6)/6 (66.7)	1 (3.8)/1 (100)
Pagani et al [11]	33	Mixed	47 ± 11	Adults	70	22 (67)	20 (61)	65	12 (36.4)	10 (30.3)/8 (80)	7 (21.2)/7 (100)
Rastan et al [4]	517	PCCS	63.5 ± 11.2	18–84	72	141 (27)	383 (74)	78.7	128 (24.8)	15 (2.9)/3 (20)	5 (1)/2 (40)
Schmidt et al [27]	220	Mixed	49 ± 16	Adults	67	–	–	320.9	–	–	–
Slottosch et al [23]	77	Mixed	60 ± 13	25–83	77	–	72 (94)	79	–	–	–
Smith et al [24]	17	PCCS	66.6 ± 13.6	37–83	76	11 (65)	14 (82)	86	7 (41.2)	–	–
Unosawa et al [25]	47	PCCS	64.4 ± 12.5	22–83	74	32 (68)	39 (83)	63.5	14 (29.8)	–	–
Wang et al [5]	62	PCCS	51 ± 15	Adults	52	–	19 (31)	61	34 (54.8)	–	–
Wu et al [6]	110	PCCS	60 ± 14	Adults	71	–	–	143.3	46 (41.8)	–	–
Wu et al [13]	60	Mixed	51.33	19–83	67	–	44 (73)	97.3	32 (53.3)	–	3 (5)/2 (66.7)
Zhang et al [7]	32	PCCS	55.4 ± 11.9	30–75	56	17 (53)	–	64.8	8 (25.0)	–	–

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CA = cardiac arrest; D/C = hospital discharge; ECMO = extracorporeal membrane oxygenation; HTP = heart transplant; IABP = intraaortic balloon pump; Mixed = mixed population; N/A = not applicable; PCCS = postcardiotomy cardiogenic shock; VAD = ventricular assist device.

The overall mortality observations from this meta-analysis are confirmed by cumulative data submitted to the ELSO Registry between 1990 and 2013[h] which is presented in the following table:

Table 12: Survival Data from Patients submitted to the ELSO Registry: 1990-2013[h]

		Survive ECLS		Survive to DC	
	Total, n	n	%	n	%
Neonatal					
Respiratory	26,583	22,452	84	19,818	75
Cardiac	5,159	3,165	61	2,078	40
ECPR	914	585	64	358	39
Pediatric					
Respiratory	5,923	3,881	66	3,359	57
Cardiac	6,459	4,203	65	3,197	49
ECPR	1,878	1,023	54	770	41
Adult					
Respiratory	4,382	2,800	64	2,439	56
Cardiac	3,431	1,877	55	1,349	40
ECPR	969	358	37	267	28
Total	55,668	40,344	72	33,635	60

(From the Extracorporeal Life Support Organization Registry, reprinted with permission.)
DC, discharge; ECLS, extracorporeal life support; ECPR, extracorporeal membrane oxygenation–assisted CPR.

[h] Bartlett RH. Jour Amer Coll Surgeons 2014;218:317-327

Rapid recovery of cardiac a respiratory and neurologic function consistent with life and the adequacy (acidosis) and duration of support are the primary determinants of the ability to successfully wean from support in the acute phase (0-7 days). Major disadvantages of ECMO are the need for anticoagulation and the requirement of high amounts of transfused blood products which increases the systemic inflammatory response that is induced by the initial surgery, the ECMO components, and cardiogenic shock itself. Neurologic (hemorrhagic and ischemic or embolic), bleeding complications (including transfusion requirements), complications of ECMO and limb complications of peripheral cannulation are also significant sources of additional major morbidity in the acute phase. Single ventricle pediatric patients generally fare worse than those post two ventricle repairs. A meta-analysis of 1,886 patients by Cheng et al. summarizes the major complications of adult ECMO for cardiogenic shock and cardiac arrest as follows.[g]

Table 13: Rates of Complications of veno-arterial ECMO in postcardiotomy cardiogenic shock and cardia arrest[g]

Table 2. Rates of Complications of Venoarterial Extracorporeal Membrane Oxygenation in Cardiogenic Shock and Cardiac Arrest

Complications	Number of Studies	Reported Rate Minimum, Maximum (%)	Cumulative Complication Rate	Cochran's Q	*p* Value Heterogeneity	I-Squared (%)	Pooled Estimate Rate (%)	95% Confidence Interval (%)
LEI	13	3.7, 37.5	112 of 677	29.2	0.004	58.9	16.9	12.5–22.6
LEF	5	5.4, 20.7	33 of 335	4.4	0.350	9.9	10.3	7.3–14.5
LEA	5	0, 8.1	7 of 192	2.4	0.658	0	4.7	2.3–9.3
Stroke	3	3.9, 9.7	36 of 630	2.1	0.346	5.9	5.9	4.2–8.3
Neurologic	9	5.9, 22.1	151 of 1,019	18.4	0.018	56.5	13.3	9.9–17.7
AKI	6	29.9, 86.7	197 of 380	64.9	<0.001	92.3	55.6	35.5–74.0
Requiring RRT	15	7.84, 86.7	758 of 1,452	138.0	<0.001	89.9	46.0	36.7–55.5
Bleeding	5	14.8, 63.6	120 of 260	22.0	<0.001	81.8	40.8	26.8–56.6
Re-Thx for bleed	6	16.1, 86.7	409 of 828	86.9	<0.001	94.2	41.9	24.3–61.8
Significant infection	10	13.7, 64.5	321 of 922	130.6	<0.001	93.1	30.4	19.5–44.0

AKI = acute kidney injury; LEA = lower extremity amputation; LEF = lower extremity fasciotomy or compartment syndrome; LEI = lower extremity ischemia; Re-Thx = rethoracotomy for bleeding or tamponade; RRT = renal replacement therapy.

Data from the ELSO Registry (**Table 14**) shows that for the most common types of complications reported, the overall incidence of each is remarkably similar in the adult (defined by ELSO as > 16years) and pediatric populations (0-16 years) with the exception of intracranial hemorrhage (ICH) where a substantially higher incidence is observed in the ELSO defined pediatric age groups

Table 14: Summary of major complications by age reported to the ELSO Registry following cardiac related uses: 1990-2013[h]

	0–30 Days	31 Days and <1 year	1 Year and <16 years	>16 Years
Mechanical				
Oxygenator failure	7.1 (25)	8 (30)	8.6 (44)	12.2 (36)
Tubing rupture	0.5 (32)	0.6 (19)	1.2 (34)	0.2 (38)
Pump malfunction	1.6 (30)	2 (34)	2 (50)	0.7 (38)
Cannula problems	6 (33)	5.5 (38)	6.3 (44)	4.5 (31)
Patient related				
ICH	11.2 (23)	5.9 (29)	4 (19)	2 (8)
Cannula site bleeding	10.5 (31)	12.1 (39)	17.9 (54)	19.6 (40)
Surgical site bleeding	31.3 (31)	32.8 (39)	28.5 (48)	23.7 (34)
Cardiac tamponade	6 (28)	5.3 (35)	5.1 (50)	5.5 (30)
Clinical seizures	7.1 (31)	8.7 (26)	4.4 (21)	2 (22)

Table entries are in percentage reported (% survival). ECLS, extra-corporeal life support; ICH, intracranial hemorrhage.

Once weaned, the function of multiple organ systems (e.g., residual cardiac and respiratory function; immune, renal and neurologic function) are significant determinants of post-wean and total discharge mortality outcomes in both populations.

Multiple case series support the notion that after 5-7 days of ECMO support, patients rarely demonstrate additional recovery of cardiocirculatory function and ECMO-related complications begin to increase exponentially. Thus, Fisher,[i] Pagani,[j] and Smediera et al.[d] recommend that ECMO weaning be forced or a transition to durable VAD be made after a 48-72 hour interval because additional recovery becomes unlikely.

Furthermore, the reported mortality outcome results, as summarized by Cheng et al.[g] in their meta-analysis, have been consistent over time (1990-2012). High mortality has continued to plague temporary cardiopulmonary and circulatory support with ECMO. The available data suggests that despite progress in intensive care management[k] and ECMO hardware components,[l,k] in-hospital mortality has not significantly changed during the last decade. Most notably, 2 separate analyses of postcardiotomy CS patients undergoing ECMO at the Cleveland Clinic in the two distinct time periods of 1992-2000

[i] Fiser SM et al. Ann Thorac Surg 2001;71:210
[j] Pagani FD et al. Ann Thorac Surg 2001;71(Suppl):S77
[k] Rastan et al. J Thorac Cardiovasc Surg 2010;139:302-311
[l] Pokersnik JA et al. Card Surg 2012;27:246-252

and 2005-2010 showed no differences in overall successful wean or bridge to VAD or Transplant rates (57% vs.55%; time period 1 vs. 2, respectively) or overall survival to discharge over time (35 vs. 33%; time period 1 vs. 2,respectively). In addition, Pokersnik et al.[l] have also shown that in the recent era, overall wean and survival rates are unaffected by differences in 3 different key circuit component combinations of centrifugal pumps and hollow fiber oxygenators (Medtronic pump and oxygenator; Medtronic pump and Sorin oxygenator; Sorin pump and Oxygenator). Evolution in ECMO technology has improved the ease with which PCS patients are cared for but has done little to impact overall survival rates.

ECMO Supported Cardiopulmonary Resuscitation (E-CPR)

Survival to hospital discharge for adult in-patient cardiac arrest resuscitated with conventional CPR therapies has been shown to be poor. A report of adult in-hospital cardiac arrest outcomes from the National Registry of Cardiopulmonary Resuscitation containing data from 14,720 events reported a survival rate of 17%.[m] Determinants of outcome included age greater than 60 years, underlying primary disease, cardiac asystole or pulseless electrical activity as the initial rhythm, absence of severe comorbidities, location of cardiac arrest outside of monitored environments, cardiac arrests occurring during regular working hours, and quality of CPR administered.

Survival after ECMO supported Cardiopulmonary Resuscitation (E-CPR) is variably reported in terms of patient populations to which it has been applied (e.g. witnessed or non-witnessed arrest, in and out of hospital arrest, etc), the duration of conventional CPR prior to the decision to initiate of ECMO Assistance (10-60 minutes), the time to actual initiation of ECMO support, and the routes of access (Trans femoral vs. Carotid/jugular access, vs. sternotomy access). In addition, maintaining an trained on-site E-CPR team is expensive and not universally available. As a result, the ultimate value of E-CPR as a proven therapeutic strategy for failed prolonged CPR in adults is largely unknown. Although the use of E-CPR in adults has increased over time, improvements in survival with increasing experience have not been observed. In fact, a retrospective analysis of the Extracorporeal Life Support (ELSO) Registry for adult patients treated with E-CPR found a significant trend toward increased mortality in the recent years.[28] . As reflected in the ELSO experience, literature reports of survival to hospital discharge in patients undergoing E-CPR fall within a relatively consistent range throughout the literature of approximately 25-45% (27% overall in ELSO registry).[28]

[m] Peberdy MA et al. Resuscitation 2003;58:297–308

Factors associated with improved survival for E-CPR patients in the ELSO experience (295 patients, 1992-2007) included shorter duration of CPR, primary cardiac diagnosis, in-hospital cardiac arrest, reversible reason for cardiac arrest, cause of cardiac arrest amenable to interventions such as coronary revascularization in patients with myocardial infarction, absence of lactic acidosis prior to ECMO, and absence of ECMO complications such as renal failure, multisystem organ failure, and neurologic injury. Use of peripheral cannulation also predicted lower mortality and neurologic complication rates in the ELSO experience.

Chen et al.[n] performed a 3-year prospective observational study on patients aged 18 –75 years with witnessed in-hospital cardiac arrest of cardiac origin undergoing conventional CPR of more than 10 minutes. Outcomes in patients where E-CPR was initiated at this time point were compared to outcomes in patients receiving continued conventional CPR. A matching process based on propensity-score was done to equalize potential prognostic factors in both groups, and to formulate a balanced 1:1 matched cohort study. The primary endpoint was survival to hospital discharge, and analysis was by intention to treat. This study was registered with ClinicalTrials.gov, number NCT00173615.

Of the 975 patients with in-hospital cardiac arrest events recorded during the 36-month observational study, 113 received conventional CPR and 59 received ECMO supported CPR, who met the selection criteria. Unmatched patients who underwent ECMO supported CPR had a higher survival rate to discharge (log-rank p<0.0001) and a better 1-year survival than those who received conventional CPR (log rank p=0.007). The propensity score-matching process selected 46 patients from the ECMO supported CPR-M group and 46 from the conventional CPR-M group for further analysis. Between the propensity-score matched groups, there was still a significant difference in survival to discharge (hazard ratio [HR] 0.51, 95% CI 0.35-0.74, p<0·0001), 30-day survival (HR 0.47, 95% CI 0.28–0.77, p=0.003), and 1-year survival (HR 0.53, 95% CI 0.33l0.83, p=0.006) favoring ECMO supported CPR over conventional CPR.[n]

[n] Chen YS et al. Lancet 2008; 372: 554–61

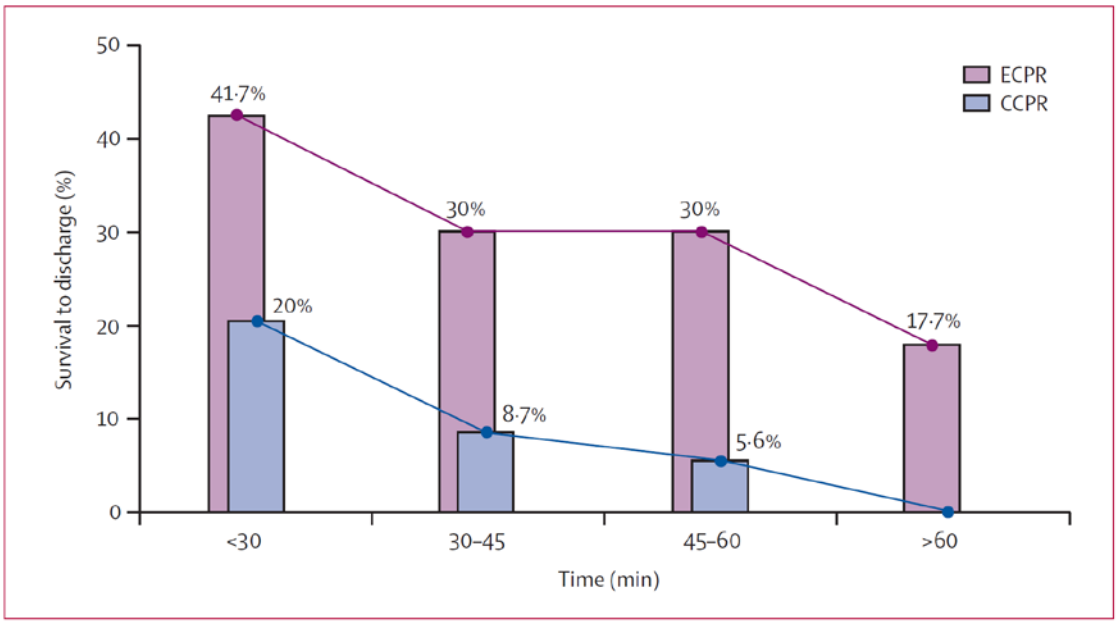


Figure 6: **Relation between CPR duration and the survival rate to discharge From Chen YS et al.** **(**ECPR=extracorporeal CPR. CCPR=conventional CPR).

In Chen's analysis, factors significantly associated with poor prognosis (higher mortality) included longer CPR duration and pulseless electrical activity or asystole. These observations regarding the association of short CPR duration and survival indicate that institutions wishing to obtain optimal outcomes by deploying ECMO support to aid failed CPR should have readily available skilled personnel to assemble the ECMO circuit and deploy ECMO support at all times.

From the adult reports reviewed, other overall factors associated with improved survival for E-CPR patients included shorter duration of CPR, primary cardiac diagnosis, in-hospital cardiac arrest, reversible reason for cardiac arrest, cause of cardiac arrest amenable to interventions such as coronary revascularization in patients with myocardial infarction, absence of lactic acidosis prior to ECMO, and absence of ECMO complications such as renal failure, multisystem organ failure, and neurologic injury.

Neurologic injury during ECMO precludes good outcomes among patients who use ECMO support for any indication. In patients using E-CPR, the risk of central nervous system (CNS) injury following CPR may be added to the risk of CNS injury posed by ECMO support. Analysis of adult ELSO data found that 33% of patients undergoing E-CPR had a post-procedure diagnosis of CNS injury and 21% met criteria for brain death.[27]. Patients meeting brain death criteria were withdrawn early from ECMO.

Whether brain death in these patients occurred during CPR or during ECMO is not certain.

Clinical Conclusion - Cardiopulmonary

Acute catastrophic cardiogenic shock resulting in pump failure and/or cardiac arrest is a condition incompatible with life and results in the need for acute restoration of cardiopulmonary function. Efforts to determine the cause of the underlying failure at this point become secondary. As a therapeutic strategy, early use of ECMO in patients with acute catastrophic cardiogenic shock (i.e,. failed CPR, post-cardiotomy failure to wean) is clinically indicated for salvage therapy based on review of experience accumulated over the last 3 decades. ECMO use in these circumstances results in a low but predictable rate of salvage that is not achievable using standard of care therapy.

Patients with acute catastrophic cardiogenic shock despite optimal medical treatment face almost certain death, and all treatment alternatives have to be assessed in the light of an otherwise dismal prognosis. ECMO allows rapid restoration of circulation during primary cardiac surgery or active resuscitation, fits with almost all patients and clinical scenarios, offers varying cannulation options, and covers abnormalities in biventricular function and lung function. The last is of substantial importance in active resuscitation secondary to surgery and emergency operations where the underlying reason for acute catastrophic cardiogenic shock cannot be completely fixed, and following failed CPR where significant bi-ventricular stunning may have occurred. In these cases, ECMO allows bridging of patients for further evaluation and decision-making and judgment of neurologic status. ECMO can only provide short-term circulatory support that is often inadequate for successful bridge to transplantation. However, ECMO may serve an important role as an acute rescue modality in patients with heart disease presenting with acute cardiogenic shock or cardiac arrest prior to VAD implantation.

Given the lack of effective alternative treatments and the alternative outcome of almost certain death without therapy, there is no equipoise for clinical evaluation of ECMO when used for these specific purposes. Even if it were possible, the anecdotal reports available and their consistency over decades of use argue against the value of randomized trials for generation of additional confirmatory data and do not suggest trials designed specifically to determine results of ECMO for these indications will yield results different from those already observed.

Clinical Indications - Adult Respiratory Failure

Acute respiratory distress syndrome (ARDS) is a distinct type of respiratory failure characterized by alveolar flooding, atelectasis, decreased lung compliance and severe gas exchange abnormalities. ARDS complicates a variety of illnesses including pneumonia of various etiologies, sepsis, aspiration, severe trauma, and massive transfusion. ARDS due to these varying etiologies results in the same clinical, physiologic, and pathologic features. The management of ARDS is the same regardless of the inciting event.

There is limited data in the literature regarding the use of ECMO for adult pulmonary indications. There has been one randomized controlled trial of ECMO for severe ARDS since studies by Zapol[o] in 1979 and Morris[p] in 1994. This was the CESAR trial which evaluated ECMO for severe ARDS compared to controls. As previously noted, the CESAR trial demonstrated reduced mortality in the ECMO group; however, 25% of patients that were referred to the ECMO center did not receive ECMO. Since publication of the CESAR trial there has been a resurgence in the use of ECMO particularly for severe H1N1 influenza associated respiratory failure.

Standard of Care

The standard therapy for respiratory failure and ARDS includes supportive care, oxygenation, and treatment of the underlying inciting condition(s). Care is usually provided in an intensive care unit setting. The majority of ARDS patients require mechanical ventilation. Since the publication of the ARMA Trial[q], a lung protective ventilation (LPV) strategy has become the standard of care for mechanical ventilator support in ARDS. The ARMA Trial was a randomized, controlled trial which demonstrated reduced mortality (31% vs. 40%) in ARDS patients randomized to low tidal volume (6ml/kg) ventilation compared to conventional ventilation (12 ml/kg). Subsequent meta-analyses have also demonstrated improved 28 day and hospital

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[o] Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 1979; 242:2193–6

[p] Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF, Weaver LK, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;149:295–305

[q] Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000; 342(18):1301

mortality.[r] Despite this important advance in mechanical ventilation, ARDS still represents a treatment challenge and rescue therapies (including recruitment maneuvers, inhaled nitric oxide, and prone positioning) are still needed in up to 35% of patients.[s]

Severe Acute Respiratory Distress Syndrome (ARDS) due to multiple etiologies (pneumonia, H1N1 influenza, sepsis, trauma, etc.)

As already noted in the literature section above, seven articles were identified with relevant data on the use of ECMO for ARDS in adults including one meta-analysis,[29] one RCT,[20] and five case series.[7,11,14,16,19] Survival to discharge ranged from 45%[14] to 84%.[16] The Zampieri meta-analysis[29] demonstrated in-hospital survival for ECMO patients ranging from 50% to 76% whereas for non-ECMO patients, it ranged from 50% to 60%. ECMO patients had lower odds of in-hospital mortality. This pooled odds ratio (OR) was obtained from the results from the cohort analyses using propensity scores (PS) and matching ECMO and non-ECMO patients without replacement (where a matched non-ECMO control patient cannot be used again to serve as a control for another ECMO patient). This PS matching method is a more conservative approach compared to using replacement because it avoids the potential error of a control patient dying yet being counted more than once in the study. When the pooled OR was estimated using PS with replacement, it showed a statistically significant decrease in in-hospital mortality (OR 0.52; 95% CI 0.35 - 0.76).

From the results of the Zampieri meta-analysis[29] the impact of ECMO on hospital mortality remains unclear. The CESAR RCT was conducted in the UK and all ECMO patients were referred to a single expert treatment center. Out of the 90 patients that were randomly allocated to ECMO, 75% actually received ECMO treatment but 25% did not receive ECMO. Six-month survival without disability and risk of dying was much better among ECMO-allocated patients compared to those that received conventional ventilation. A limitation of the CESAR trial included in the meta-analysis was the lack of standardization of the conventional ventilation (control) arm which was conducted at a separate center from the ECMO arm. There also may have been a referral bias effect in that 22 patients (25%) from the CESAR trial were referred for ECMO but did not actually receive ECMO treatment at the treatment center.

The other 2 case series (Noah 2011 and Pham 2013) included in this meta-analysis are also limited by their small size and the use of propensity matched historical

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[r] AU Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P.Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann Intern Med. 2009;151(8):566

[s] Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, et al. Positive end expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008;299:646–55

controls. While the Noah study reported better outcomes for ECMO the Pham study reported no benefit**.** The Pham study included 30 ICUs where ECMO was used in France. Many of the ECMO and control patients in the Pham study were managed concurrently in the same centers. In contrast, the Noah study as well as CESAR trial transferred the ECMO patients to a referral center. Propensity scoring may not control for all confounders and carries a risk of unrecognized imbalance in baseline severity. Age is one such potential confounder particularly in case series of H1N1 ECMO therapy. The ECMO treated H1N1 patients from both the Noah and Pham studies tended to be younger and were more likely to survive solely due to age.

Linden et al.,[11] evaluated long term data of ECMO survivors in Sweden. Outcome data included survival to hospital discharge and after discharge of 37 ECMO patients. This study demonstrated a high survival rate to hospital discharge (70%) and the majority of survivors were able to return to work in the same occupation as before ECMO. While this study offers a window into the long term effects of ECMO on survivors the sample size is quite small. More studies on the long term effects of ECMO are needed given the high morbidity and mortality associated with this therapy.

As already noted, miniaturized ECMO was evaluated by Müller[14] and Haneya.[7] These studies demonstrated high rates of survival but significant mortality due to multi-organ failure. There was also a high rate of ECMO circuit complications in the Haneya case series; surgical site bleeding and thrombosis of the oxygenator were observed in the Muller study. The Haneya study is limited by its small sample size (22) and single center nature. The study population was heterogeneous with respect to etiology of lung injury including 5 trauma/post-surgery patients. Potential candidates were transported to the referral center for ECMO while unstable patients were started on ECMO at the referring site. As with the CESAR trial there may have been bias related to transport to an expert center. The Müller study population consisted of mostly community acquired and aspiration pneumonia with a few cases of sepsis and trauma induced ARDS. The Müller study is limited by the lack of a control group for comparison and the single center nature.

Influenza A (H1N1)

As already noted, ECMO use for the treatment of ARDS due to H1N1 infection in adults was identified in two cohorts,[15,21] one case series with data from the ELSO registry,[17] and an additional four case series studies[6,9,19 ,26](Appendix B). These studies have demonstrated improved survival; however, caution must be taken when interpreting these results. As already noted above, the subjects in the CESAR trial may have experienced referral center bias. In addition, the Noah study demonstrated improved mortality compared to propensity score matched controls; however, the Pham study demonstrated no benefit despite also using rigorous propensity score matching of controls. The Italian case series did not have a comparison to a matched control population. The other case series studies[6,9,27] identified in our literature review had very small sample sizes (less than

15) and reported survival to hospital discharge rates ranging from 36% to 92% (Appendix B).

Data from five of the studies[9,15,19,21,26] demonstrated that the common major causes of death were multi-organ failure (MOF), cerebral hemorrhage, refractory hypoxemia, refractory shock, septic shock, acute renal failure, and infection (Appendix B). ECMO-related complications were high in two studies (one cohort[22] and one case series[9]) at 53% and 62%, respectively. The most common complications observed in ECMO use for ARDS due to H1N1 infection were disseminated intravascular coagulation, massive bleeding, epistaxis, and cannulation-site bleeding. ECMO circuit complications included cannula-site infection and/or septicemia, cannulation complications, oxygenator failures, and blood clots (Appendix B).

Pneumonia

The CESAR trial included over 50% of subjects with ARDS due to pneumonia of various etiologies. While the CESAR trial demonstrated a mortality benefit compared to conventional therapy the limitations of the study have already been noted above. One case series from South Korea[18] evaluated the use of ECMO for respiratory failure due to pneumonia (12/18) or ARDS (6/18) in patients who received orthotopic liver transplantation. Eight patients were weaned from ECMO after a mean of 11 days; however, 55% (10) died of overwhelming infection. Survival to hospital discharge and at one year was 33% (4/12). The major cause of death in this study was multiple organ dysfunction (MOF) due to sepsis. Combined with data on ECMO in ARDS there is still insufficient evidence regarding the effectiveness of ECMO for the indication of adult pneumonia.

Bridge to Lung Transplant

Shafii et al.[24] evaluated 13 usual interstitial pneumonia patients that were placed on ECMO (62% on VV-ECMO) with the intent to use it as a bridge-to-transplant (BTT). A total of 9 (69%) patients, all receiving double lung transplant, survived. The rest of the patients died before transplant (2) or after double (1) or single (1) lung transplant. ECMO bridged patients experienced a considerably higher rate of major complications (renal failure, sepsis, disseminated intravascular coagulation (DIC), MOF) and had longer hospital courses post-transplant compared to the non-ECMO patients. While ECMO may be used as a bridge to transplant it is fraught with high morbidity. The current evidence is limited in establishing effectiveness for the indication of bridge to lung transplant and the long term outcomes of ECMO in this population remain uncharacterized.

Graft dysfunction after lung transplantation

Hartwig et al. evaluated the use of ECMO for severe primary graft dysfunction following single or double lung transplantation and was the only study identified for this indication.[8] ECMO was used as a salvage therapy for failure to wean off cardiopulmonary bypass due to pulmonary failure. Among 28 transplants, survival rates

at 30 days, one year, and 5 years were 82%, 64%, and 49%, respectively. The ECMO group experienced a high rate of blood stream infections at 90 days. Bacterial infection was observed in 36% (10) of the ECMO patients compared to controls (12%), p = 0.001. Freedom from bronchiolitis obliterans syndrome was 88% at 3 years. There is insufficient evidence regarding the effectiveness of ECMO therapy in post-transplant primary graft dysfunction.

Clinical Conclusion - Respiratory

The current evidence is inconclusive regarding the benefits of ECMO for adult respiratory failure. While the results of the Zampieri meta-analysis[30] favors a mortality reduction for ECMO treated patients compared to non-ECMO treated patients independent of the matching technique used, the individual studies included in the analysis had several limitations as already noted above. In addition, the majority of the studies evaluating ECMO use for the indications for use assessed in this literature review were case series and did not include control groups. The lack of a control comparison limits the interpretability of the results as data on survival and complications related to ECMO use cannot be attributable to the actual use of the device vs. the patient population, who already are at high risk for death due to other complications. One small case series evaluated the use of ECMO as a bridge to transplant and another small case series evaluated ECMO for post-lung transplant primary graft dysfunction (PGD), while other individual case series evaluated mobile ECMO devices, and ECMO for refractory septic shock. Only the CESAR trial was an RCT where over 50% of subjects in both arms had ARDS due to pneumonia and, as noted above, there are significant confounding issues that impact the interpretation of the CESAR trial results. An additional consideration is that only two (7%) of the studies were conducted among patients from the United States.[8,25] Caution should be taken when extrapolating the results from all of the studies to patients from the United States as the patients, patient selection criteria for ECMO, and/or health care system may differ across countries.

In summary, for H1N1 influenza induced ARDS there may be equipoise between VV ECMO and continued conventional medical therapy which includes lung protective ventilation. However, there have been few studies (with several limitations) to date of ECMO in adult respiratory failure, the majority of which are only case series. The long term outcomes in adult survivors of ECMO therapy for ARDS remain poorly characterized. ECMO is associated with increased risk and morbidity. More randomized controlled trials are needed to further evaluate the benefits of ECMO in adult respiratory failure/ARDS given the serious risks associated with ECMO and the availability of lung protective ventilation and other rescue therapies.

FDA Considerations and Conclusions

After a review and evaluation of the adult ECMO literature, FDA believes that the original Proposed Order (published January 8, 2013) identifying conditions where

imminent death is threatened by cardiopulmonary failure in neonates and infants [i.e., pediatric patient population], or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery [in all patient populations] remains a viable candidate for reclassification to Class II. FDA would like Panel input regarding the evidence presented today in support of the safety and effectiveness for the use of ECMO in all other conditions (e.g., adult respiratory failure).

APPENDIX A

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Appendix B

Publications Included in Literature Review

Veno-Arterial Extracorporeal Membrane Oxygenator (VA-ECMO)

Failure to Wean

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
Loforte, 2012[12]	Case Series January 2007 - July 2011 Italy 64% male 100% MV	n = 50	64.3 (Range 40 - 84)	VA: 100%	10.9 days (Range 2 - 36)	*Survival to hospital discharge:* 19 (38%) *Bridged to LVAD* 1 (2%) *Major causes of death:* MOF 19 (38%) Sepsis 9 (18%) Cerebral hemorrhage 9 (18%) *Complications*: Transfusion 50 (100%) Bleeding/tamponade 29 (58%) Liver failure 21 (42%) Pulmonary complications 12 (24%) Leg ischemia 4 (8%)

[1] ECMO or otherwise specified

Abbreviations: ECMO: Extracorporeal Membrane Oxygenation; IQR: Interquartile Range; LVAD: Left Ventricular Assist Device; SD: Standard Deviation; MOF: Multiple Organ Failure; MV: Mechanical Ventilation; VA: Veno-arterial; VV: Veno-venous.

Acute Onset Refractory Cardiogenic Shock

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD median [IQR]	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
Barth, 2012[4]	Case Series July 2004 - December 2009 France 100% male Mean follow-up was 2 ± 0.5 years [1 – 2.6].	n = 242 HUHT n=8	HUHT 41 ± 8 [Range 24 - 54]	VA: 100%	Before HUHT 6.3 ± 4.6 days [Range 1 - 14]	*Bridge-to-:* Nothing: 90; survival to discharge: 40 (44%) – *Major causes of death:* ▪ Mainly MOF or neurological damage owing to cardiac arrest LVAD: 5 – Destination therapy: 3; survival to discharge: 3 (100%) – Heart transplant: 2; survival to discharge: 2 (100%) – LVAD from HUHT list: 3; survival to discharge: 3 (100%) HUHT: 8; 1-year survival: 8 (100%) - Sedated and mechanically ventilated: 4 (50%) - Length of MV: 4.7 ± 5.6 days - ECMO-associated complications: One patient had a femoral bleeding requiring surgery and another patient had an ischemic lower limb because of a distal perfusion catheter thrombosis, leading to septic shock and amputation. - *Complications*: ▪ One patient presented a primary graft dysfunction needing post-transplantation ECMO for five days. ▪ Two patients required an IABP

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD median [IQR]	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
						for 24 hours. ▪ Massive post-operative bleeding with tamponade: 1 (12.5%) ▪ Bleeding from the ECMO cannulation site: 4 (50%). ▪ RBC: 9.6 ± 9.3 units. ▪ Renal failure: 4 (50%), 1 needed hemofiltration. ▪ Transient vascular ischemic accident without cardiac thrombi: 1 (12.5%) ▪ Infectious complications: 4 (50%) - Status at follow-up: ▪ Working and engaged in sports: 3 (37.5%) ▪ Retired with good level of physical activity: 1 (12.5%) ▪ Symptomatic: 3 (37.5%) ▪ Unknown functional capacity: 1 (12.5%)
Schmidt, 2012[23]	Case Series January 2003 – December 2009 France 67% male 100% patients received MV during course of ECMO, but at ECMO initiation, 7 patients were not mechanically ventilated	n = 220	48.9 ± 15.8	VA: 100%	Non-infected patients 8 ± 5 days Infected patients 16 ± 17 days (p< .0001)	*Nosocomial infections:* 142 (64.5%)

<table>
<tr><th>First Author
Year</th><th>Study Design
Population</th><th>Sample Size
(ECMO)[1]</th><th>Age
mean ± SD
median [IQR]</th><th>VV or VA</th><th>Duration of Support
mean ± SD
median [IQR]</th><th>Relevant Safety Results</th></tr>
<tr><td>Loforte,2012[12]</td><td>Case Series

January 2007 - July 2011

Italy

75.3% male

100% MV</td><td>n = 73</td><td>60.3 ± 11.6
(Range 23 – 84)</td><td>VA: 100%</td><td>10.9 ± 7.6 days
(Range 2 - 34)</td><td>Survival to hospital discharge: 33 (45.2%)
Bridge to LVAD 3 (4%)
Survival after LVAD 1 (33%)

Major causes of death:
<table><tr><td>MOF</td><td>26 (35.6%)</td></tr><tr><td>Sepsis</td><td>11 (15.1%)</td></tr><tr><td>Cerebral hemorrhage</td><td>11 (15.1%)</td></tr></table>
Complications:
<table><tr><td>Transfusion</td><td>73 (100%)</td></tr><tr><td>Bleeding/tamponade</td><td>37 (50.7%)</td></tr><tr><td>Liver failure</td><td>30 (41.1%)</td></tr><tr><td>Pulmonary complications</td><td>16 (21.9%)</td></tr></table></td></tr>
<tr><td>Wang, 2009[28]</td><td>Case Series

January 2004 – May 2008

China

52% male

MV: 81 ± 86 hours</td><td>n = 62</td><td>51 ± 15</td><td>VA: 100%</td><td>61 ± 37 hours</td><td>Survival to hospital discharge: 34 (55%)
4-year survival: 32 (52%)

4-year quality of life outcomes:
The mean scores after cardiac surgery were similar for the ECMO survivors and the patients who did not receive ECMO support (12,644 patients), except that the vitality and mental health scores were statistically significantly lower among the ECMO survivors (p<0.05).

Major causes of death:
<table><tr><td>MOF due to sepsis</td><td>13 (46%)</td></tr><tr><td>Heart failure without any improvement in cardiac function</td><td>11 (39%)</td></tr></table></td></tr>
</table>

<table>
<tr><th>First Author
Year</th><th>Study Design
Population</th><th>Sample Size
(ECMO)[1]</th><th>Age
mean ± SD
median [IQR]</th><th>VV or VA</th><th>Duration of Support
mean ± SD
median [IQR]</th><th>Relevant Safety Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Cerebral infarction and bleeding</td><td>2 (7%)</td></tr>
<tr><td>Disseminated intravascular coagulation</td><td>2 (7%)</td></tr>
</table>
Major causes of death:
<table>
<tr><td>MOF due to sepsis</td><td>13 (46%)</td></tr>
<tr><td>Heart failure without any improvement in cardiac function</td><td>11 (39%)</td></tr>
<tr><td>Cerebral infarction and bleeding</td><td>2 (7%)</td></tr>
<tr><td>Disseminated intravascular coagulation</td><td>2 (7%)</td></tr>
</table>
Complications:
<table>
<tr><td>Renal failure</td><td>23 (37%)</td></tr>
<tr><td>Infection</td><td>19 (31%)</td></tr>
<tr><td>Rethoracotomy</td><td>10 (16%)</td></tr>
<tr><td>Neurologic complication</td><td>8 (13%)</td></tr>
<tr><td>Ischemia of the lower limbs</td><td>5 (8%)</td></tr>
<tr><td>Leg amputation</td><td>1 (2%)</td></tr>
<tr><td>RBC transfusion</td><td>19.8 ± 1.8 units</td></tr>
</table>
ECMO circuit complications:
<table>
<tr><td>Change of oxygenator</td><td>11 (18%)</td></tr>
</table>
</td></tr>
<tr><td>Aissaoui, 2011[2]</td><td>Case Series

March 2007 – March 2008

France

66% male</td><td>n = 51</td><td>54 ± 14</td><td>VA: 100%</td><td>Weaned
8 ± 6 days

Not Weaned
4 ± 2 days</td><td>30-day survival: 29 (57%)

Bridge-to-:
Nothing: 20; 30-day survival: 19 (95%)
VAD: 6; 30-day survival: 5 (83%)
Transplant: 6; 30-day survival: 5 (83%)

Major causes of death among 19 in-hospital</td></tr>
</table>

<table>
<tr><th>First Author
Year</th><th>Study Design
Population</th><th>Sample Size
(ECMO)[1]</th><th>Age
mean ± SD
median [IQR]</th><th>VV or VA</th><th>Duration of Support
mean ± SD
median [IQR]</th><th>Relevant Safety Results</th></tr>
<tr><td></td><td>22% Transferred from other centers

18% experienced cardiac arrest during the 12 hours preceding ECMO

14% were cannulated under continuous CPR</td><td></td><td></td><td></td><td></td><td>deaths:
<table><tr><td>MOF</td><td>15 (79%)</td></tr><tr><td>Brain death</td><td>4 (21%)</td></tr></table>
Complications:
<table><tr><td>Renal replacement therapy</td><td>16 (31%)</td></tr><tr><td>Major bleeding</td><td>13 (25%)</td></tr><tr><td>Pulmonary edema</td><td>7 (14%)</td></tr><tr><td>Surgical wound infection</td><td>3 (6%)</td></tr><tr><td>Stroke</td><td>3 (6%)</td></tr><tr><td>Arterial ischemia</td><td>2 (4%)</td></tr></table></td></tr>
<tr><td>Hsu, 2010[10]</td><td>Case Series

January 2002 - December 2006

Taiwan

71% male</td><td>n = 51</td><td>63 ± 15.7</td><td>VA: 100%</td><td>7.5 ± 6.7 days</td><td>Survival to hospital discharge: 17 (33%)
30-day survival: 26 (51%)
1-year survival: 15 (29%)

Bridge-to-transplant: 4; 1-year survival: 3 (75%)

Major causes of death:
After weaning from ECMO (N=10):
- Pulmonary infections 6 (60%)
- Refractory congestive heart failure: 4 (40%)

Not able to wean from ECMO (N=24):
- MOF: 20 (83%)

Complications:
<table><tr><td>Acute renal failure</td><td>38 (75%)</td></tr><tr><td>Femoral bleeding</td><td>20 (39%)</td></tr><tr><td>Haematuria</td><td>17 (33%)</td></tr><tr><td>Gastrointestinal bleeding</td><td>13 (25%)</td></tr><tr><td>Pulmonary infection</td><td>11 (22%)</td></tr><tr><td>Compartment syndrome</td><td>5 (10%)</td></tr><tr><td>ARDS</td><td>5 (10%)</td></tr></table></td></tr>
</table>

<table>
<tr><th>First Author
Year</th><th>Study Design
Population</th><th>Sample Size
(ECMO)[1]</th><th>Age
mean ± SD
median [IQR]</th><th>VV or VA</th><th>Duration of Support
mean ± SD
median [IQR]</th><th>Relevant Safety Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Limb ischaemia</td><td>3 (6%)</td></tr>
<tr><td>Neurologic complications</td><td>3 (6%)</td></tr>
<tr><td>Catheter-related infection</td><td>3 (6%)</td></tr>
<tr><td>Leg amputation</td><td>2 (4%)</td></tr>
<tr><td>Pancreatitis</td><td>1 (2%)</td></tr>
</table>
</td></tr>
<tr><td>Bakhtiary, 2008[3]</td><td>Case Series

January 2003 - November 2006

Germany

78% male

69% preoperative CPR</td><td>n = 45</td><td>60 ± 14</td><td>VA: 100%</td><td>6.4 ± 4.5 days</td><td>
Survival to discharge: 13 (29%)
30-day survival: 21 (47%)
3-year survival: 10 (22%)

Bridge-to-:
- Nothing: 38; Survival to discharge: 9 (24%)
- LVAD: 5; Survival to discharge: 3 (60%)
▪ Deaths from MOF: 2 (40%)
- Transplants: 2 (1 heart and 1 concomitant heart–lung). Survival to discharge: 1 (heart) (50%).
▪ Heart-lung patient died from MOF

Major causes of death:
- After weaning from ECMO (N=25):
▪ Pulmonary infections and sepsis with consecutive MOF: 12 (48%)

- Not able to wean from ECMO (N=20):
▪ Persistent heart failure without any improvement in cardiac function: 18 (90%)

Complications:
<table>
<tr><td>Renal failure</td><td>39 (86.7%)</td></tr>
</table>
</td></tr>
</table>

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD median [IQR]	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
						Continuous VV hemodialysis: 39 (86.7%) Systemic infection: 26 (58%) Neurologic complications: 4 (8.9%) Cerebral hemorrhage: 3 (7%) Stroke: 1 (2%) Rethoracotomy for bleeding or tamponade: 39 (86.7%) Ischemia of lower limbs: 3 (7%) Fasciotomy: 6 (13%) ARDS: 4 (9%) Leg amputation: 1 (2%) Change of oxygenator: 4 (9%)
Sakamoto, 2012[22]	Case Series January 2000 – December 2010 Japan 66% male (Gender results include 64 cardiac arrest patients from the total study (n=98))	n = 34	72 ± 12 48% ≥ 75 Age results include 64 cardiac arrest patients from the total study (n=98)	VA: 100%	Not reported for RCS patients only	*Survival to hospital discharge:* 14 (44%)
Luo, 2009[13]	Case Series February 2005 - June 2008 China 68% male Low tidal volume MV with biphasic positive airway pressure	n = 31	50.4 ± 14.8	VA: 100%	132.1 ± 118.5 hours	*Survival to hospital discharge:* 18 (58%) Bridge to transplant 1 (3%) *Major causes of death:* MOF and heart failure without any improvement in cardiac function *Complications*: Infections: 11 (36%) Rethoracotomy: 11 (36%) Renal failure need CRRT: 10 (32%)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD median [IQR]	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
						Neurologic events: 3 (10%) Ischemia of lower limb: 2 (7%) Fasciotomy: 2 (7%) Bowel ischemia: 1 (3%) *ECMO circuit complications:* Change of oxygenator: 4 (13%)
Bréchot, 2013[5]	Case Series January 2008 – September 2011 France 50% male RCS due to bacterial septic shock	n = 14	48 ± 13	VA: 100% Switched to VV: 5 (36%) for persistent severe respiratory failure	Survivors 5.5 days (Range 2–12) Non-survivors 3 days (Range 1–7) Switched to VV 5 days (Range 3–21)	*Survival to hospital discharge:* 10 (71%) *Survival after hospital discharge (median follow-up of 13 (3–43) months):* 10 (71%) *Major causes of death:* MOF: 2 (50%) Secondary septic shock: 2 (50%) *Complications (unknown if n=14 or n=10)*: One or more major ECMO-related complications: 60% Leg ischemia/leg amputation: 1 Surgical wound infections: 3 Ischemic stroke: 1 Severe distal ischemia/ purpura fulminans/ amputation: 2

[1] ECMO or otherwise specified

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; CPR: Cardiopulmonary Resuscitation; ECMO: Extracorporeal Membrane Oxygenation; HUHT: High Urgency Heart Transplant; IABP: Intra-Aortic Balloon Pump Counterpulsation; IQR: Interquartile Range; LVAD: Left Ventricular Assist Device; MOF: Multiple Organ Failure; MV: Mechanical Ventilation; RBC: Red Blood Cell; RCS: Refractory Cardiogenic Shock; SD: Standard Deviation; VA: Veno-arterial; VAD: Ventricular Assist Device; VV: Veno-venous.

Extracorporeal Cardiopulmonary Resuscitation (ECPR)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
Shin, 2011[25]	Case-Control Study (Propensity score-matched) January 2003 - June 2009 South Korea 62% male	ECPR n = 85 CPR n = 321 propensity score-matched n= 120	ECPR 59.9 ± 15.3 CPR 61.6 ± 14.2	VA: 100%	ECPR 42.1 ± 25.7 mins CPR 41.3 ± 36.7 mins	*In-hospital survival (ECPR):* 19 (31.7%) *In-hospital survival (CPR):* 6 (10%) (p<0.05) *6-month survival (ECPR):* 19 (31.7%) *6-month survival (CPR):* 5 (8.3%) (p<0.05) *In-hospital survival with minimal neurologic impairment* - Covariate-adjusted OR: 0.06 95% CI (0.008–0.54) - Propensity score-adjusted OR: 0.17 95% CI (0.04–0.71) *6-month survival with minimal neurologic impairment* - Covariate-adjusted HR: 0.38 95% CI (0.19–0.77) - Propensity score-adjusted HR: 0.50 95% CI (0.30–0.84)
Thiagarajan, 2009[27]	Case Series ELSO registry 1992 - 2007 66% male 75% had cardiac disease	n = 295	52 [35 – 64]	VA: 91% VV: 3% Both: 5%	67 [21 -133]	*Survival to hospital discharge:* 1992–1995 1 (25%) *Total* 4 1996–1999 6 (22%) 27 2000–2003 41 (41%) 101 2004–2007 31 (19%) 163 *Complications* – Neurologic complications: 98 (33%) ▪ Brain death: 61 (21%) ▪ Highest in the recent years 2004 to 2007 (26%) compared to 1992

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<tr><td></td><td></td><td></td><td></td><td></td><td></td><td>to 1999 (16%) and 2000 to 2003 (p<0.03)
- Need for renal replacement therapy increased odds of mortality (OR: 2.41; (95% CI: 1.34 to 4.34)

ECMO circuit complications:
<table><tr><th></th><th>Survived</th><th>Died</th></tr><tr><td>Mechanical problems</td><td>22 (28%)</td><td>73 (34%)</td></tr><tr><td>Clots in the ECMO circuit</td><td>13 (17%)</td><td>43 (20%)</td></tr><tr><td>Air embolus</td><td>1 (1%)</td><td>4 (2%)</td></tr><tr><td>Cannula site bleeding</td><td>15 (19%)</td><td>46 (21%)</td></tr><tr><td>Surgical bleeding</td><td>17 (22%)</td><td>54 (25%)</td></tr></table></td></tr>
<tr><td>Sakamoto, 2012[22]</td><td>Case Series

January 2000 – December 2010

66% male (Gender results include 64 cardiac arrest patients from the total study (n=98))</td><td>n = 64</td><td>72 ± 12

Age results include 34 cardiac arrest patients from the total study (n=98))</td><td>VA: 100%</td><td>Not reported for cardiac arrest patients only</td><td>Survival to hospital discharge: 18 (56%)</td></tr>
<tr><td>Schmidt, 2012[23]</td><td>Case Series

January 2003 – December 2009

France

67% male (Gender results include other RCS patients from the total study (n=220))

100% patients received mechanical ventilation</td><td>n = 28</td><td>49 ± 16

Age results include other RCS patients from the total study (n=220))</td><td>VA: 100%</td><td>Not reported for cardiac arrest patients only</td><td>Nosocomial infections: 17 (61%)</td></tr>
</table>

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
	during course of ECMO, but at ECMO initiation, 7 patients were not mechanically ventilated					

[1] ECMO or otherwise specified

Abbreviations: Abbreviations: CPR: Cardiopulmonary Resuscitation; ECMO: Extracorporeal Membrane Oxygenation; ECPR: Extracorporeal Cardiopulmonary Resuscitation; ELSO: Extracorporeal Life Support Organization; HR: Hazard Ratio; IQR: Interquartile Range; LVAD: Left Ventricular Assist Device; OR: Odds Ratio; RCS: Refractory Cardiogenic Shock; SD: Standard Deviation; MOF: Multiple Organ Failure; VA: Veno-arterial; VV: Veno-venous.

Veno-Venous Extracorporeal Membrane Oxygenator (VV-ECMO)

Acute Respiratory Distress Syndrome (ARDS)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD median [IQR]	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
Zampieri, 2013[29]	Meta-analysis One RCT (60% pneumonia) Two Cohort studies (100% H1N1) 2001 – 2010 Protective mechanical ventilation was used in the control group, and ultraprotective MV was used in the ECMO-supported group. ECMO group used a polymethylpentene extracorporeal lung membrane.	ECMO n=179 3 (2%) N=174	ECMO 36.5 ± 11.4 to 45 ± 13 Non-ECMO 38.5 ± 13 to 45 ± 15	Two studies: VV: 100% One study: VV: 87% VA: 13%	9 days [IQR 6 - 16] to 11 days [IQR 8 - 22] Not reported in one study	*In-hospital mortality (ECMO vs. Control):* PS matching without replacement: OR:0.71 (95% CI 0.34 - 1.47) PS matching with replacement: (OR 0.52; 95% CI 0.35 - 0.76) – Peek, 2009 ▪ OR:0.58 (95% CI 0.31 - 1.11) – Noah, 2011: ▪ OR: 0.40 (95% CI 0.16 - 1.00) – Pham, 2012: ▪ OR: 1.48 (95% CI 0.68 - 3.21) *In-hospital survival (ECMO vs. Control):* – Peek, 2009: ▪ 43/68 (63%) vs. 45/90 (50%) – Noah, 2011: ▪ 45/59 (76%) vs. 18/32 (56%) – Pham, 2012: ▪ 26/52 (50%) vs. 31/52 (60%) These results include data from the cohort studies with propensity scores estimated without replacement of matched patients
Peek, 2009[20]	Randomized Clinical Trial 2000-2006	ECMO n=90	ECMO 39.9 ± 13·4	VV: 100%	9 days [6 –16]	*6-month survival without disability (ECMO vs. Control):* 57/90 (63%) vs. 41/87 (47%) (3 patients did not have information about

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median [IQR]</th><th>Relevant Safety Results</th></tr>
<tr><td></td><td>United Kingdom

75% patients actually received ECMO</td><td>Control
n=90</td><td>Control
40·4 ± 13·4</td><td></td><td></td><td>severe disability)

Death or severe disability at 6-months after randomization (ECMO vs. Control):
RR:0.69 (95% CI 0.5 - 0.97)

Major causes of death:<table><tr><th></th><th>ECMO</th><th>Control</th></tr><tr><td>Respiratory failure</td><td>8 (9%)</td><td>24 (27%)</td></tr><tr><td>MOF</td><td>14 (16%)</td><td>15 (17%)</td></tr><tr><td>Neurological disorder</td><td>4 (4%)</td><td>2 (2%)</td></tr><tr><td>Cardiovascular disorder</td><td>1 (1%)</td><td>3 (3%)</td></tr><tr><td>ECMO-related</td><td>1 (1%)</td><td>-</td></tr><tr><td>Other</td><td>1 (1%)</td><td>0</td></tr><tr><td>Unknown</td><td>4 (4%)</td><td>1 (1%)</td></tr></table></td></tr>
<tr><td>Müller, 2009[14]</td><td>Case Series

April 2006 - December 2008.

Germany

Miniaturized ECMO

75% male

<u>ARDS Caused by:</u>
Pneumonia: 25
Aspiration: 11
Sepsis: 15
Multiple Trauma: 4
Other: 5
Two patients did not fulfill definition for ARDS but</td><td>n= 60</td><td>53
[21 to 78]</td><td>VV: 100%
Converted to VA: 1.6%</td><td>9 days [5 to 13]</td><td>Survival to discharge: 27 (45%)

Major causes of death:<table><tr><td>Intractable septic shock/MOF</td><td>27 (81%)</td></tr><tr><td>Cardiac failure</td><td>3 (10%)</td></tr><tr><td>Pulmonary and/or cerebral hemorrhage</td><td>2 (6%)</td></tr></table>
Complications:<table><tr><td>Surgical Site Bleeding</td><td>11 (18%)</td></tr><tr><td>Diffuse Bleeding</td><td>5 (8.3%)</td></tr><tr><td>Femoral Vein Thrombosis</td><td>5 (8.3%)</td></tr><tr><td>Pulmonary Hemorrhage</td><td>3 (5%)</td></tr><tr><td>Cannulation Site Bleeding</td><td>2 (3.3%)</td></tr></table>
Accidental dislocation of backflow cannula leading to rapid asystole due to hypoxia</td></tr>
</table>

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD median [IQR]	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
	are included in results. >70% transferred from other hospital Acute Renal Failure: 28 (47%)					(n=1) Resuscitation during implantation (n=2) *ECMO circuit complications:* Thrombosis of Oxygenator: 10 (17%) Failure of Pump Head: 1 (1.6%)
Linden, 2009 [11]	Case Series 62-month study Sweden 57% male 100% patients received MV	n = 37	40 (Range 21 - 65)	Not reported	345 hours (Range 65 - 1238)	*Survival to hospital discharge*: 26 (70%) *Post-discharge Survival*: 21 (51%) Status at follow- up (Mean: 26 months (Range 12 – 50): Sixteen (76%) back in same occupation as before ECMO, 2 (9.5%) retired, 2 (9.5%) on disability, and 1 (5%) receiving medical rehabilitation. - All patients living at home. - No patients were in need of extra oxygen. HRQoL results (n=15 survivors): - "Most patients had reduced health related quality of life (HRQoL), according to the SGRQ, but were stating less respiratory symptoms than conventionally treated ARDS patients in previous studies."
Haneya, 2012[7]	Case Series May 2010 - July 2011 Germany	n = 22	47 [36 to 61]	VV: 100%	13 days [8 to 19]	*Survival to hospital discharge*: 15 (68.2%) *ECMO related complications: 0 (0%)* *Major causes of death:*

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD median [IQR]	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
	Cardiohelp portable miniaturized ECMO Transport on ECMO (%): Total: 15 (68.2) Ambulance: 2 Helicopter: 13 Two patients were initially supported with another ECMO system and switched due to circuit thrombus formation. 82% male Diagnosis leading to ARDS (%) Pneumonia 14 (63.6) Trauma/Post-surgery 5 (22.7) H1N1 3 (13.7) Acute renal failure before ECMO: 3 (13.7%)					MOF/Sepsis: 6 (27%) MOF: 1 (4.5%) *ECMO circuit complications:* Circuit thrombus formation necessitating device exchange: 9 (41%)
Noah,2013[16]	Case Series October 2000 - September 2010 United Kingdom Patients with severe respiratory failure caused by confirmed *Legionella* who failed to respond to conventional intensive care management 58% male 68% patients with tracheostomy	n = 19	50 [46.5 – 59]	VV: 100%	8 days [6 – 10] (Range 3 – 30)	*Survived at hospital discharge:* 16 (84%) *Major causes of death:* MOF: 2 (10.5%) Intracranial hemorrhage: 1 (5%) *Hemorrhagic complications:* Cardiac tamponade: 1 Chest drain-related hemorrhage: 1 Gastrointestinal bleeding: 1 Tracheostomy site bleed: 1 Intracranial hemorrhage: 1

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD median [IQR]	VV or VA	Duration of Support mean ± SD median [IQR]	Relevant Safety Results
Patroniti, 2011[19]	Case Series August 2009 - March 2010 Italy 73% male	n = 11	44 [35–55]	VV: 98% VA: 2% (not specified if this patient population or H1N1-infected patients)	8 days [3–21]	Survival to discharge: 6 (54%) *Causes of death:* MOF due to sepsis: 2 (40%) Septic shock: 2 (40%) Neurological disorder: 1 (20%) *ECMO related complications:* None reported among these patients.

[1] ECMO or otherwise specified

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; ECMO: Extracorporeal Membrane Oxygenation; HRQoL: Health-Related Quality Of Life; IQR: Interquartile Range; LVAD: Left Ventricular Assist Device; MOF: Multiple Organ Failure; MV: Mechanical Ventilation; OR: Odds Ratio; PS: Propensity Score; SD: Standard Deviation; SGRQ: St George's Respiratory Questionnaire; VA: Veno-arterial; VV: Veno-venous.

Influenza A (H1N1)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD	VV or VA	Duration of Support mean ± SD	Relevant Safety Results
Pham, 2013[21]	Cohort Study July 2009 – March 2010 France 87.4% patients with H1N1-confirmed infection Both groups received MV Propensity score (PS) matching variables: Age; sex; pregnancy status; BMI; risk factors for influenza-related complications as defined by CDC (immunosuppression, chronic lung disease, diabetes, chronic renal failure, chronic heart failure, obesity, Simplified Acute Physiology Score 3 score, Sequential Organ Failure Assessment score, bacterial co-infection, and shock at the time of admission); and the use of corticosteroids at the time of admission or of a rescue therapy, worst arterial pH, ratio of PaO_2 to FiO_2, and Lung Injury Score before ECMO implantation or during the first week for non-ECMO patients with ARDS.	ECMO n=123 Propensity score matched n=52 Non-ECMO n=157 Propensity score matched n=52	ECMO 45 ± 13 Non-ECMO 45 ± 15	VV: 87% VA: 13%	11 days [8 - 22]	*In-hospital survival (ECMO vs. Control):* 26/52 (50%) vs. 31/52 (60%) PS matching without replacement: OR: 1.48 (95% CI 0.68 - 3.21) PS matching with replacement: OR: 0.45 (95% CI 0.25–0.78) *Causes of death:* MOF: 22 (50%) Refractory hypoxemia: 8 (18%) Refractory shock: 6 (14%) Intracranial hemorrhage: 5 (11%) Unspecified: 3 (7%) One or more ECMO-related complications: 65 (53%) *Complications:* *Bleeding and heparin-related* Epistaxis: 15 (12%) Cannulation-site bleeding: 10 (8%) Suspected heparin-induced thrombocytopenia: 8 (7%) Gastrointestinal hemorrhage/ hemoperitoneum: 7 (6%) Hemothorax: 7 (6%) Hemoptysis: 5 (4%) Hemorrhagic shock: 5 (4%) Intra-cranial hemorrhage: 5 (4%) *ECMO circuit complications (n=123):* Cannula-site infection and/or septicemia: 14 (11%)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD	VV or VA	Duration of Support mean ± SD	Relevant Safety Results
						Deep vein thrombosis: 8 (7%) Hemolysis: 8 (7%) ECMO circuit failure (2 membrane dysfunction, 1 cannula mobilization, 1 circuit thrombosis, 1 cardiac arrest while changing cannula): 5 (4%) Acute leg ischemia: 2 (2%) Vascular wound or dissection: 3 (2%)
Noah, 2011[15]	Cohort Study Winter 2009 – 2010 United Kingdom 80 ECMO-referred patients: 11 (13.8%) did not received ECMO 37.5 % male 100% confirmed or suspected H1N1 infection 86.4% confirmed H1N1 infection among individual matched patients. 89% confirmed H1N1 infection among propensity/GenMatch matched patients. Ultraprotective MV was used among ECMO patients. Unknown whether lung protective MV was used among non-ECMO patients. Individual case matching variables: (1) the number of days of continuous MV; (2) FiO_2 associated with the arterial blood gas with the lowest PaO_2; (3) ratio of PaO_2 to FiO_2 from the	ECMO N=80 Individual matching n=59 Propensity score matching n=75 GenMatch n=75 Non-ECMO Individual matching n=59 Propensity score matching n=75	ECMO 36.5 ± 11.4 Non-ECMO 42.8 ± 13.4	VV: 83.8% VA: 16.2% (One patient converted to VV on day 3)	9 days [6 - 12]	*In-hospital mortality (ECMO vs. Control):* Individual matching RR: 0.45 (95% CI 0.26 – 0.79) Propensity score matching RR: 0.51 (95% CI 0.31 – 0.84) GenMatch RR: 0.47 (95% CI 0.31 – 0.72) *In-hospital survival (ECMO vs. Control):* Individual matching ▪ 45/59 (76.3%) vs. 18/32 (47.5%) (p<0.01) Propensity score matching ▪ 57/75 (76%) vs. 40/75 (53.3%) (p<0.01) GenMatch ▪ 57/75 (76%) vs. 37/75 (49.3%) (p<0.01) "The mean RRs of death for ECMO-referred patients vs non–ECMO-referred patients remained between 0.4 and 0.6 when the analyses were restricted to patients with confirmed H1N1 infection; ECMO-referred patients receiving ECMO;

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mean ± SD</th><th>Relevant Safety Results</th></tr>
<tr><td></td><td>arterial blood gas with the lowest PaO_2; (4) Sequential Organ Failure Assessment Score; (5) age; (6) pregnancy status; and (7) BMI category.

Propensity score matching variables:
(1) the number of days of continuous MV; (2) FiO_2; (3) ratio of PaO_2 to FiO_2; (4) Sequential Organ Failure Assessment Score; (5) pregnancy; (6) BMI category; (7) H1N1 status (suspected or confirmed) (8) prior use of inhaled nitric oxide, high frequency oscillation, or prone positioning; (9) advanced cardiovascular support; (10)renal support; (11) antiviral therapy; and (12) age.

GenMatch matching was based on the propensity score and the same individual covariates included in the propensity score model.</td><td>GenMatch
n=75</td><td></td><td></td><td></td><td>and patients with an FIO_2 of 1.0.

Causes of death:
<table><tr><td>Cerebral hemorrhage</td><td>7 (9%)</td></tr><tr><td>MOF</td><td>3 (4%)</td></tr><tr><td>Irrecoverable lung damage</td><td>2 (3%)</td></tr><tr><td>Precannulation cardiac arrest</td><td>1 (1%)</td></tr><tr><td>Massive pulmonary hemorrhage</td><td>1 (1%)</td></tr><tr><td>Neutropenic sepsis</td><td>1 (1%)</td></tr><tr><td>Rhabdomyolysis</td><td>1 (1%)</td></tr></table>
Four patients died after being transferred back to the referring hospital (1 had pulmonary embolism, 1 had cerebrovascular accident, and 2 had MOF), and 2 died after being managed without ECMO (1 intracranial and 1 pulmonary hemorrhage).</td></tr>
<tr><td>Paden, 2013[17]</td><td>ELSO registry

International

Adult respiratory failure patients with novel H1N1 treated with ECMO.</td><td>n=237
Unknown if H1N1 confirmed</td><td>Not stated</td><td>VV: 100%</td><td>Not stated</td><td>Survival to hospital discharge: 159 (67%)</td></tr>
<tr><td>Patroniti, 2011[19]</td><td>Case Series

August 2009 - March 2010

Italy

Patients with severe ARDS with confirmed H1N1 One pregnant and three puerperal patients (n = 4,</td><td>n = 49</td><td>39 [32–46]</td><td>VV in all but one patient (VA). It is not stated whether the VA patient was confirmed</td><td>10 days [7–17]</td><td>Survival:
ICU discharge: 35 (71%)
Hospital discharge: 35 (71%)

Causes of death:
MOF due to sepsis: 8 (57.2%)
Septic shock: 3 (21.2%)
Neurological disorder: 1 (7.2%)</td></tr>
</table>

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<tr><td></td><td>8%)

57% male

VV in all but one patient (VA). It is not stated whether the VA patient was confirmed H1N1.</td><td></td><td></td><td>H1N1.</td><td></td><td>Acute liver failure: 1 (7.2%)
Right heart failure: 1 (7.2%)

ECMO related complications (all in H1N1 patients):
- CNS hemorrhage resulting in death, two days after cannulation: n=1
- Abdominal bleeding NOT resulting in death: n=2
- Airways bleeding NOT resulting in death: n=1
- Cannulation complications NOT resulting in death: n=4</td></tr>
<tr><td>Takeda, 2012[26]</td><td>Case Series
April 2010 - March 2011
Japan
85.7% male
Pregnant: n=1

It is not stated if or how H1N1 was confirmed.
First time using ECMO for 5 facilities

None of the facilities had extensive experience administering ECMO.

None of the patients had underlying chronic respiratory failure, chronic heart failure, or immunological diseases.

All patients received anti-influenza drugs.</td><td>n= 14</td><td>54 [43–60]</td><td>VV: 100%</td><td>8.5 [4.0–10.8]</td><td>Survived at hospital discharge: 5 (35.7%)

Major causes of death:
<table><tr><td>Acute renal failure</td><td>5</td></tr><tr><td>Infection</td><td>4</td></tr><tr><td>Acute hepatic failure</td><td>3</td></tr><tr><td>Shock</td><td>3</td></tr></table>
“Excluding 1 patient who died on the first day of ECMO therapy, all patients developed adverse events associated with ECMO (92.9%).”

ECMO circuit complications 11(78.6%):
<table><tr><td>Oxygenator failures</td><td>7 (58%)</td></tr><tr><td>Blood clot</td><td>4 (28.6%)</td></tr><tr><td>Oxygenator</td><td>3 (21.4%)</td></tr><tr><td>Cannula-related problems</td><td>3 (21.4%)</td></tr><tr><td>Other circuit</td><td>1 (7.1%)</td></tr><tr><td>Pump head complications</td><td>1 (7.1%)</td></tr></table>
Complications 12 (85.7%):</td></tr>
</table>

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD	VV or VA	Duration of Support mean ± SD	Relevant Safety Results
						<table><tr><td>Disseminated intravascular coagulation</td><td>10 (71%)</td></tr><tr><td>Massive Bleeding</td><td>8 (57%)</td></tr><tr><td>Surgical site bleeding</td><td>4 (28.6%)</td></tr><tr><td>Upper digestive tract hemorrhage</td><td>4 (28.6%)</td></tr><tr><td>Cannulation site bleeding</td><td>2 (14%)</td></tr><tr><td>Hemolysis</td><td>2 (14%)</td></tr><tr><td>Venous thrombus</td><td>2 (14%)</td></tr><tr><td>Pulmonary hemorrhage</td><td>1 (7.1%)</td></tr></table>
Holzgraefe, 2010[9]	Case Series July 20, 2009 and January 12, 2010 Sweden Patients with confirmed H1N1 and severe respiratory failure 61.5% male Female: 5 (3 pregnant prior to cannulation, 2 pregnant prior to decannulation) Five previously healthy patients. Transported on ECMO: 12 (2 international). All transported patients cannulated at referring hospital. Ambulance: 7; Aircraft: 5. <u>Indications for ECMO:</u> Severe hypoxemia: 11 Pneumothoraces in combination with hypoxemia: 1 Respiratory and circulatory failure: 1	n=13	31 [25 – 50]	VV: 12 (4 converted to VA) VA: 1 (5 total) Of 5 VA, 4 were converted back to VV	16 days [9.5 - 30.5]	*Survival to hospital discharge:* 12 (92%) *3-months survival:* 12 (92%) Intrauterine survival: 2 Fetal death: 1 infant death after 18 days of the mother's ECMO treatment <u>Deaths:</u> 1 death occurred 4 days after decannulation/discharge due to intracranial hemorrhage. 27 circuit-related complications requiring intervention occurred in 8 patients (62%). None caused harm. Accidental liver puncture leading to hemorrhage and laparotomy: 1 (occurred during fluid drainage puncture attempt)

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD	VV or VA	Duration of Support mean ± SD	Relevant Safety Results
Chenaitia, 2011[6]	Case Series August 2009 to January 2010 France Patients with severe ARDS/H1N1 requiring interhospital transfer using a mobile respiratory assistance unit (MRAU) providing VV ECMO; 36% male <u>Transport:</u> Helicopter: 27% Ambulance: 73% No complication occurred during transport.	n=11 Unknown if H1N1 confirmed	33 [19.5–50]	VV: 100%	Not stated	*Survival to hospital discharge:* 5 (45.5%) *30-day survival:* 4 (35%)

[1] ECMO or otherwise specified

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; BMI: body mass index; CDC: Centers for Disease Control and Prevention; CNS: Central Nervous System; ECMO: Extracorporeal Membrane Oxygenation; FiO_2: Fraction of Inspired Oxygen; IQR: Interquartile Range; LVAD: Left Ventricular Assist Device; MOF: Multiple Organ Failure; MV: Mechanical Ventilation; PaO_2: Partial Pressure of Oxygen in Arterial Blood; SD: Standard Deviation; VA: Veno-arterial; VV: Veno-venous.

Pneumonia

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD	VV or VA	Duration of Support mean ± SD	Relevant Safety Results
Park, 2012[18]	Case series January 2008 - March 2011 South Korea 82% males 100% MV with concurrent nitric oxide	n = 12 Liver transplant patients	43 - 63	VV: 100%	2 - 28 days	*Survival to hospital discharge:* 4 (36%) *1-year survival: 4 (36%)* Continuous mechanical ventilatory support after weaning from ECMO: 4 (100%) *Major causes of death:* MOF due to sepsis

[1] ECMO or otherwise specified

Abbreviations: ECMO: Extracorporeal Membrane Oxygenation; IQR: Interquartile Range; MOF: Multiple Organ Failure; MV: Mechanical Ventilation; SD: Standard Deviation; VA: Veno-arterial; VV: Veno-venous.

Graft dysfunction after lung transplantation

First Author Year	Study Design Population	Sample Size (ECMO)[1]	Age mean ± SD	VV or VA	Duration of Support mean ± SD	Relevant Safety Results
Hartwig, 2012[8]	Case Series November 2001 - December 2009 United States Patients who underwent single-lung or bilateral-lung 25 (89%) transplantation 50% male <u>Underlying condition:</u> Interstitial pulmonary fibrosis: 11 (39%) Other: 7 (25%) COPD/A1A deficiency: 5 (18%) Cystic Fibrosis/bronchiectasis: 5 (18%)	n = 28 transplants (unit of analysis is transplants, not patients; re-do transplants are included)	Median: 51	VV: 100%	3.6 days [0.2 - 7.6]	*30-day survival:* 82% 1-year *survival:* 64% *3-year survival:* 49% *5-year survival:* 49% 90-Day blood stream infections: 10 (36%) Freedom from bronchiolitis obliterans syndrome was 88% at 3 years.
Shafii, 2012[24]	Case Series May 2008 - December 2011 United States Patients placed on ECMO with the intent to BTT. 13 usual interstitial pneumonia (UIP) patients 61.5% male DLTx recipients: 10 SLTx recipients: 1	n = 13	48.15 ± 5.63	VA: 38.46% VV: 61.54%	6.3 ± 5.5 days	DLTx survived: 9/13 (69%) DLTx expired: 1/13 (8%) SLTx expired: 1/13 (8%) Expired before transplant: 2/13 (15%) CVA: 1 (8%) Sepsis/DIC: 1 (8%)

[1] ECMO or otherwise specified

Abbreviations: Abbreviations: BTT: Bridge to Transplant; COPD: Chronic Obstructive Pulmonary Disease; CVA: Cerebrovascular Accident; DIC: Diffuse Intravascular Coagulopathy; DLTx: Double Lung Transplant; ECMO: Extracorporeal Membrane Oxygenation; IQR: Interquartile Range; SD: Standard Deviation; SLTx: Single Lung Transplant; VA: Veno-arterial; VV: Veno-venous.

APPENDIX C

MeSH Search Terms

The search for published literature was conducted on December 16, 2013 using PubMed. The search terms used were:

> ("Extracorporeal Membrane Oxygenation"[MAJR] AND ("humans"[MeSH Terms] AND English[lang] AND ("adult"[MeSH Terms])) AND (((postcardiotomy AND shock) OR (cardiac surgery AND postoperative) OR (failure to wean OR failure to separate OR (failure AND (wean* OR separate)))) OR refractory OR "Shock, Cardiogenic"[Mesh] OR "Cardiopulmonary Resuscitation"[Mesh] OR massive pulmonary emboli OR "Hypertension, Pulmonary"[Mesh] OR (((bridge to transplant OR bridge to decision) OR (bridge AND (transplant OR decision)))) OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Respiratory Distress Syndrome, Adult"[Mesh] OR H1N1 OR flu OR pneumonia OR influenza OR graft dysfunction lung transplant OR Extracorporeal Life Support Organization)

The search was limited to English language, humans, and adults. This search yielded 675 articles. Articles published on June 1, 2012 and thereafter were not indexed in PubMed at the time of the literature search. An additional search was conducted without using Mesh terms and with June 1, 2012 and December 16, 2013 and 25 additional articles were identified. The search terms used were:

> "(extracorporeal membrane oxygenation AND adult AND English[lang] AND (((postcardiotomy AND shock) OR (cardiac surgery AND postoperative) OR (failure to wean OR failure to separate OR (failure AND (wean* OR separate)))) OR refractory cardiogenic shock OR cardiopulmonary resuscitation OR pulmonary emboli OR massive pulmonary emboli OR pulmonary hypertension OR (pulmonary AND parenchyma*) OR (((bridge to transplant OR bridge to decision) OR (bridge AND (transplant OR decision)))) OR chronic obstructive pulmonary disease OR (ARDS OR (Acute AND Respiratory AND

Distress AND Syndrome)) OR H1N1 OR flu OR pneumonia OR influenza OR graft dysfunction lung transplant OR Extracorporeal Life Support Organization))."